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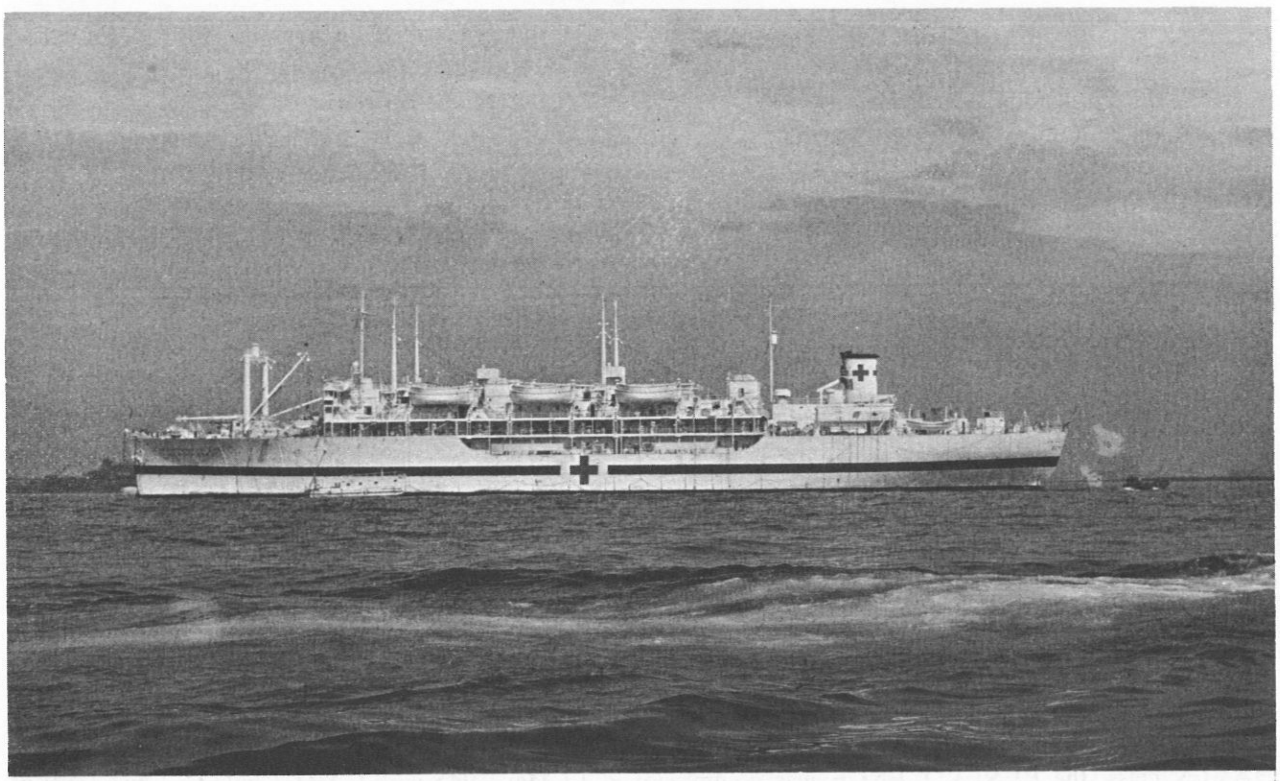

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Policy

The U.S. Navy Medical News Letter is basically an official Medical Department publication inviting the attention of officers of the Medical Department of the Regular Navy and Naval Reserve to timely up-to-date items of official and professional interest relative to medicine, dentistry, and allied sciences. The amount of information used is only that necessary to inform adequately officers of the Medical Department of the existence and source of such information. The items used are neither intended to be, nor are they, susceptible to use by any officer as a substitute for any item or article, in its original form. All readers of the News Letter are urged to obtain the original of those items of particular interest to the individual.

Change of Address

Please forward changes of address for the News Letter to Editor: Bureau of Medicine and Surgery, Navy Department, Washington, D.C. 20390 (Code 18), giving full name, rank, corps, and old and new addresses.

FRONT COVER: USS BENEVOLENCE (AH-13). One of six World War II hospital ships in the HAVEN class, the BENEVOLENCE was commissioned 12 May 1945 with CAPT Clyde C. Laws USN as commanding officer and CAPT Frederick L. McDaniel MC USN as senior medical officer. She transited the Panama Canal on 22 June and traveled via Pearl Harbor to Eniwetok where she served for 19 days as a station hospital for ships in the area, admitting 144 patients for treatment. On 12 August she rendezvoused with Task Force 38 transferring casualties from the ships 20-22 August; and then accompanied the Third Fleet, including the USS MISSOURI, to Japan where she received a total of 1,521 released prisoners of war from Japanese prison camps for physical screening and examination by 31 August, of whom 343 were admitted to the sick list. Among the patients received for screening, treatment and transfer were 60 stretcher cases in deplorable condition along with numerous cases of dysentery, beri-beri, tuberculosis, and surgical trauma. Her occupation duty continued until 27 November 1945. She was placed out of commission in reserve in 1947 and reactivated in 1950. At that time during her trial runs off San Francisco she collided with an outbound freighter (USS MARY LUCKENBACH), sinking almost immediately, 11 lives being lost. The BENEVOLENCE received one Battle Star for participation in Third Fleet operations against Japan 12-15 August 1945, and the Navy Occupation Medal for the period 2 September to 27 November 1945. This fast hospital ship had an overall length of 520 feet, a beam of 72 feet, a speed of 18 knots, and 11,141 tons displacement.

The issuance of this publication approved by the Secretary of the Navy on 4 May 1964.

THE MAIN FUNCTIONS OF THE PULMONARY CIRCULATION

By Julius H. Comroe, Jr. MD. Circulation XXXIII(1): 146-158, January 1966.
By permission of the American Heart Association, Inc.

I have chosen the title of this lecture to correct the belief of some that the pulmonary circulation has only one function; some later Conner Lecturer, however, will surely correct the assumption in my title that in 1965 we know all of the main functions of the pulmonary circulation.*

We *do* know several important functions: The first—participating in pulmonary gas exchange—has long been known. The second—serving as a blood reservoir for the left ventricle—has been known for some years but could be demonstrated quantitatively only recently. The third—providing the nutrition of the alveoli and alveolar ducts—has been uncovered in the past 2 years. The fourth—filtering particles from the mixed venous blood—sometimes results in dysfunction, but I propose to consider it instead a *function* that is sometimes abused. The fifth—removing excess fluid from the alveoli—has been known since 1873, when Colin poured 25 liters of fluid down the trachea of a horse in a 6-hour period.

Gas Exchange

The alveoli and the alveolar capillaries are magnificently designed to exchange gases; no artificial lung ever made approaches them in capacity, speed, efficiency, compactness, or durability. For teaching purposes, I have often pictured the lung by a greatly simplified schema (fig. 1). Actually it is a vast, complicated and marvelous system of branching tubes that is in itself a superb engineering job. The air tubes begin at the nose and mouth and then join to become the trachea. The trachea divides into bronchi and the bronchi divide and subdivide into bronchioles. After 18 branchings, there are several hundred thousand respiratory bronchioles and after 24 branchings the air tubes end in about 300,000,000 alveoli, where most of the gas exchange occurs. The blood tubes begin as the pulmonary trunk, divide into the right and left pulmonary arteries, which then divide into arterioles, and these in turn into hundreds of millions of alveolar capillaries. The volume of blood in these capillaries at any one time is only about 75 ml, but the total surface area of the capillaries is 70 m^2; the alveoli have a similar area for gas exchange.

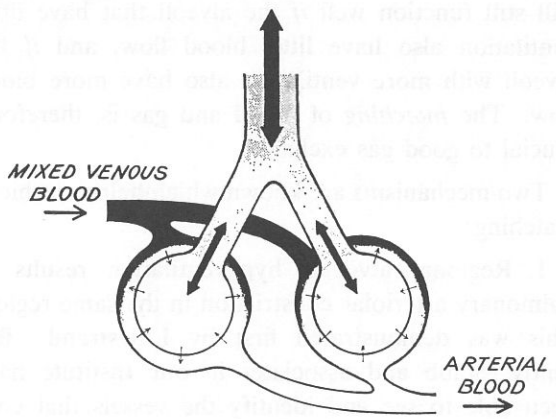

Figure 1

Schema of the lungs and pulmonary circulation. The rounded areas represent alveoli; the shaded tubes leading to them represent all of the conducting airways. Mixed venous blood (dark) flows through capillaries in intimate contact with ventilated alveoli and becomes arterial blood (light). The large arrow in the upper airway represents the tidal volume; the two smaller arrows in the lower airways and alveoli illustrate uniform distribution of the tidal volume. The fine arrows represent the transfer of O_2 and CO_2 between gas and blood.

From the Cardiovascular Research Institute, University of California San Francisco Medical Center, San Francisco, California.
The original investigations reported in this lecture were supported in part by Grant HE-06285 of U.S. Public Health Service.
The Lewis A. Conner Memorial Lecture, presented at the meeting of the American Heart Association, Miami, Florida, October 15, 1965. A slightly modified version was presented as the Annual Lecture to the Harveian Society, London, England, April 5, 1965.
*There is now a vast literature on the pulmonary circulation, which includes several recent books, reports of symposia, and scholarly review articles. Fishman's "Dynamics of the Pulmonary Circulation" (in the Handbook of Physiology, Section 2, Circulation, Volume 2, pp. 1667-1743) contains 446 references for those readers who wish further details and documentation. This Conner Lecture is not intended to be another review, but more of a personal account of recent and current work by my colleagues in the Cardiovascular Research Institute.

If the gas exchanger is an ideal one, all of the inspired gas and mixed venous blood should be distributed uniformly to these millions of gas-blood interfaces. In the systemic circulation there is need for both regional regulation (to shift blood from nonvital organs to vital organs during stress, or from inactive to active organs) and for over-all regulation (to maintain a proper pressure head to drive blood through the cerebral and coronary arteries). Is there any need for regional or overall regulation of blood flow through the pulmonary circulation? Because all of the right ventricular output must flow through the pulmonary blood tubes, these tubes, theoretically, should always offer minimal resistance to blood flow so that the work of the right ventricle is minimal.* And yet we now know that there is both regional and over-all regulation of pulmonary vascular resistance.

Regional (local) regulation seems to serve the purpose of matching gas and blood flow. If gas distribution is not uniform but blood distribution is uniform, the gas exchanger is not an ideal one; if gas distribution is uniform and the blood distribution is not, again the gas exchanger is not an ideal one. When both are nonuniform, the gas exchanger will still function well *if* the alveoli that have little ventilation also have little blood flow, and *if* the alveoli with more ventilation also have more blood flow. The *matching* of blood and gas is, therefore, crucial to good gas exchange.

Two mechanisms are known which help to achieve matching:

1. Regional alveolar hypoventilation results in pulmonary arteriolar constriction in the same region. This was demonstrated first by Liljestrand. Recently, Staub and associates in our Institute have been able to see and identify the vessels that constrict. They provided a low oxygen-high carbon dioxide mixture to one lung of an anesthetized cat and pure oxygen to the other lung; in this way they mimicked severe regional hypoventilation without significantly changing the oxygen content or tension of arterial blood and (because of the local vasoconstriction) without changing the arterial P_{co2} or pH. They then inundated both lungs simultaneously with liquid propane, freezing the lungs almost as they were in life: Sections of the still-frozen lungs clearly demonstrated constriction of arterioles in the "hypoventilated" lung and not in the other (fig. 2 not shown). This constriction reduces pulmonary blood flow to regions with reduced air flow and helps to match air and blood flow throughout both lungs. The mechanism is a local one and does not depend on nerves or reflexes.

2. Regional ischemia results in airway constriction in the same region. Severinghaus, Swenson, and associates inflated a balloon at the tip of a catheter to occlude one pulmonary artery in both dog and man. Within a few breaths, air flow decreased to the lung with its pulmonary artery occluded and increased to the other lung. Such a regional increase in airway resistance serves to direct more of the inspired air to alveoli with normal or increased blood flow and so helps to match air and blood flow to the alveoli. It is partly for this reason that some patients who have complete obstruction of some pulmonary arteries by emboli have little or no unsaturation of their arterial blood.

Because alveoli with no pulmonary capillary blood flow receive no carbon dioxide from mixed venous blood, it seemed reasonable that the bronchoconstriction might be related to low alveolar P_{co2}. This was the case because addition of 5% carbon dioxide to the inspired gas at the moment of inflating the balloon and occluding the pulmonary artery prevented the increased airway resistance, the shift of alveolar ventilation, and the matching of gas and blood. Several years ago Severinghaus and Stupfel, and later Robin and associates, believed that a low P_{co2} in mixed alveolar gas—relative to the P_{co2} of simultaneously measured arterial blood—might serve as a sensitive diagnostic test of pulmonary embolism and might even provide a quantitative measure of the proportion of the pulmonary circulation that was obstructed by emboli. Unfortunately, it is not so useful as predicted, probably because of this compensatory increase in airway resistance, which leads to a partial correction of mismatching of blood and gas that would otherwise instantaneously follow pulmonary embolism (fig. 3). The decrease in wasted ventilation helps the patient but hinders the physician in diagnosis. However, if the broncho-constriction is severe enough to be measured, *it,* instead of the difference in carbon dioxide tensions, can become the clue to pulmonary embolism.

* This is not true of the fetal circulation. In the fetus, gas exchange occurs in the placenta and it is to the advantage of the fetus to reduce pulmonary blood flow to the minimum required for maturation of the lungs; this can be achieved by general pulmonary vasoconstriction.

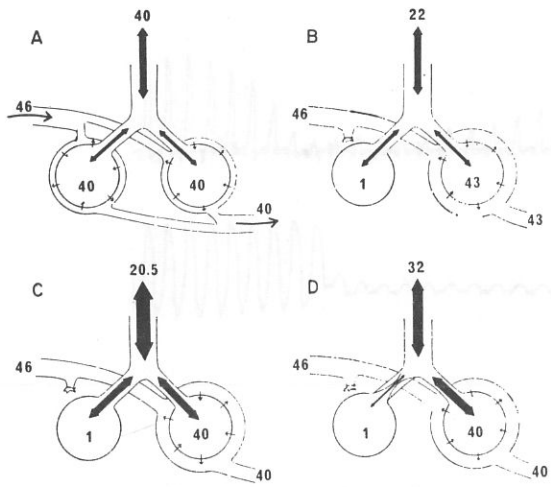

Figure 3

Effects of unilateral pulmonary artery obstruction. The schema is similar to that in figure 1; the numbers refer to the CO_2 tension in mixed venous blood, alveolar gas, mixed expired alveolar gas, and arterial blood. (A) Normal lung with uniform distribution of gas and blood; there is no difference between the CO_2 tension of arterial blood and mixed expired alveolar gas. (B) Immediate effects of occlusion of one pulmonary artery; the lung which receives the total pulmonary blood flow now has inadequate ventilation to eliminate CO_2 and alveolar and arterial CO_2 tensions increase. (C) Ventilation has increased to both lungs and maintains a normal arterial blood CO_2 tension but cannot reduce the difference between the CO_2 tension of arterial blood and mixed expired alveolar gas. (D) Bronchoconstriction has occurred in the nonperfused lung and shifts air from it to the perfused lung. Total ventilation returns toward normal and the difference between the CO_2 tension of arterial blood and mixed expired alveolar gas decreases greatly.

Blood Reservoir

The pulmonary vessels normally contain about 600 ml of blood; most of this is in readily distensible vessels. This blood and that in the left atrium together serve as a reservoir that supplies blood to fill the left ventricle and maintain its output, even when the right ventricular output falls behind for a few beats. Guz and associates have demonstrated this nicely; they placed one electromagnetic flowmeter on a pulmonary trunk and another on the ascending aorta so that they could simultaneously measure pulmonary artery flow (the inflow to the pulmonary circulation) and aortic flow (which in a steady state is the output from the pulmonary circulation). In this way they could calculate beat-by-beat the change in pulmonary blood volume. Figure 4 shows the response to completely blocking the inflow to the pulmonary circulation. The stroke volume of the left ventricle continued unchanged for two beats and then gradually declined; when the pulmonary circulation was congested and its blood volume considerably increased, left ventricular output was maintained even longer without any blood added to the pulmonary circulation.

Nutrition

Many physiologists think of the pulmonary circulation as a set of pipes, delivering blood to the alveolar capillaries, collecting it, and sending it on to the left atrium and left ventricle, but having nothing to do with nourishing the tissue through which it passes. This view was strengthened by clinical observations: Surgeons had sometimes found it necessary to tie off one pulmonary artery but still leave the lung in place. A year or two later the tissues in such lungs appeared to be healthy. There was, of course, little uptake of oxygen because there was no pulmonary circulation but the ventilation of the ischemic lung appeared to be normal. The obvious conclusion was that the pulmonary circulation is not essential for the nutrition of the pulmonary tissues, and, since *it* is not, the bronchial circulation must be. We assume that the anatomists knew better, but they were silent. Several years ago we got a rude shock. Finley, Tooley, and associates in our Institute wanted to see how long compensatory bronchoconstriction lasted after one pulmonary artery was occluded. To the surprise of no one, occlusion of one pulmonary artery for 24, 48, or 72 hours led to a decrease in ventilation to that lung, but to the surprise of everyone, this lung was atelectatic and markedly congested. Grossly and microscopically, it resembled the atelectatic lung of the newborn. But still the lung did not die and, with continued occlusion of the pulmonary artery, the ventilation of that lung increased, its appearance improved, and in 6 to 8 months it was reasonably normal in both ventilation and appearance, although somewhat scarred. The time required for its recovery seemed to be similar to the time required for the establishment of connections between the bronchial artery and the alveolar capillaries and it is a reasonable assumption that the bronchial circulation, by enlargement of existing channels or growth of new vessels, comes to the rescue of the pulmonary tissues.

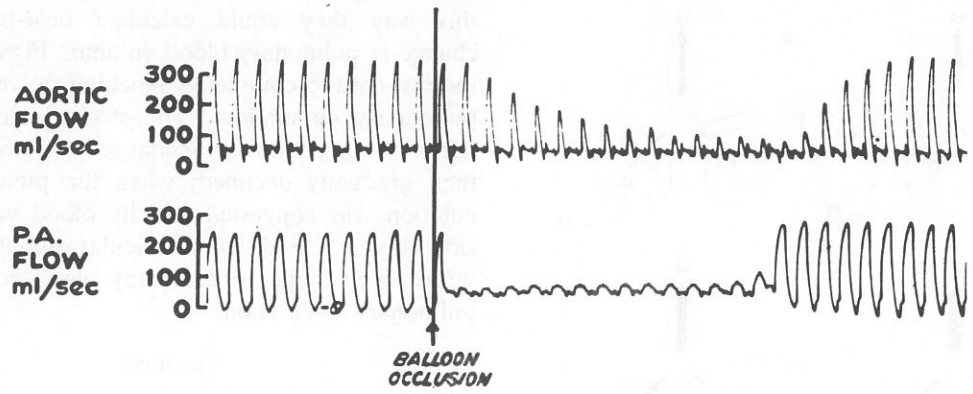

Figure 4

Response to occlusion of the main pulmonary artery by inflation of a ballon; the left ventricular output remains unchanged for two beats and then gradually decreases.

The anatomists are correct that the bronchial arteries supply the airways down to and including the terminal bronchioles and that the pulmonary artery supplies the alveoli, alveolar ducts, and respiratory bronchioles. Nadel and his associates confirmed this in their experiments which showed that drugs that constrict smooth muscle affected only the alveolar ducts when injected into a pulmonary artery, and affected only the bronchioles when injected into the bronchial arteries.

To function properly, the alveoli and alveolar ducts require a minimal amount of blood flow per minute whether it comes from the pulmonary artery or the bronchial circulation. In the dog with unilateral pulmonary artery ligation, Tooley and associates (personal communication) have estimated that this minimal flow is about 10 ml per kg of body weight per minute. If these estimates are transferred to adult man, the minimal flow would be 700 ml per minute or only about one seventh of the normal pulmonary blood flow. It is unlikely that *total* pulmonary blood flow could ever be low enough during adult life to produce bilateral pulmonary ischemia and collapse, but *regional* blood flow can be too little to sustain cell function.

When an organ becomes ischemic, those cells with a high metabolic rate suffer first. The alveolar cells of the lung have many mitochondria (fig. 5 not shown) and a high metabolic rate. They are unusually active in the synthesis of phospholipids and have a high content of phospholipids, particularly of the saturated phospholipids and of dipalmitoyl lecithin. The alveolar cells contain intracellular structures unique in human tissues—the lamellar inclusion bodies. It appears at present that these contain dipalmitoyl lecithin or a chemical closely related to it; in some way, not yet understood, this substance reaches the alveoli and lines them with a monomolecular layer. In this form it has the unique property of decreasing surface tension and preventing collapse of alveoli during expiration.*

When alveolar cells receive less than the minimal blood flow necessary for nutrition, two things can happen: (1) the quality or quantity of surfactant formed is not proper, or (2) pulmonary capillaries become leaky, plasma enters the air spaces, and plasma fibrinogen interacts with pulmonary surfactant to cause both an inactivation of surfactant and an inhibition of fibrinolysis. The result is that alveoli collapse and are filled with fibrin threads, the so-called hyaline membranes.

Although a *total* pulmonary blood flow less than the minimal required for nutrition is virtually impossible during adult life, it is possible in the newborn because there is a large bypass, the ductus arteriosus, which can accept all of the right ventric-

* Why does the surface active material, which lowers surface tension, prevent collapse of alveoli? We are accustomed to think that the elastic recoil of the lungs is due solely to recoil of stretched elastic fibers. Actually, it is also due to the surface properties of liquid—air interfaces in the 300,000,000 alveoli. Von Neergaard showed in 1929 that fluid-filled lungs, which have a fluid-fluid interface, enlarge more for a unit increase in transpulmonary pressure than air-filled lungs, which have a fluid-air interface. Since elastic fibers recoil the same amount whether alveoli are filled with fluid or filled with air, the additional recoil of air-filled lungs must be due to the surface tension effects—the tendency of tiny bubbles to become smaller. The surfactant which normally lines the alveoli is remarkable in this respect:—As the alveoli get smaller and their surface film is compressed, the surface tension decreases almost to zero and the recoil due to surface forces almost vanishes. The surfactant produced by alveolar cells is, therefore, an anti-atelectatic factor.

ular output if it is not able to go through the pulmonary circulation. Ischemia of the newborn lung might, therefore, be a cause of atelectasis or respiratory distress syndrome.

In 1964, Drs. Clements, Tooley and Klaus were convinced that the pulmonary surfactant was dipalmitoyl lecithin or a chemical very similar to it. Because of mounting evidence that loss or inactivation of dipalmitoyl lecithin was a major factor in respiratory distress syndrome of the newborn, they and five associates spent six months studying this disease at the Kandang Kerbau Hospital at the University of Singapore. This hospital was chosen because it is by far the largest maternity hospital in the world and because it is affiliated with the University of California through its International Center for Medical Research and Training. At first the group tried to propel additional dipalmitoyl lecithin into the lungs of the newborn with respiratory distress syndrome after aerosolizing it. This replacement-type of therapy helped some infants but not all. The failures were probably due to inability to propel enough material into alveoli that were already collapsed, to the inability to obtain a suitable freon propellent that was free from mild anesthetic properties, and to the presence of material in the alveoli (probably plasma fibrinogen) which inactivated some or all of the dipalmitoyl lecithin that did reach the alveolar surfaces. When they studied babies who died of respiratory distress syndrome, they found that the pulmonary circulation offered unusually great resistance to the flow of fluids through it. They then measured pulmonary blood flow in living babies and found that in those with respiratory distress syndrome it was only one third of that in healthy babies. The increased resistance to pulmonary blood flow was not due to thrombi because it returned toward normal values when pulmonary vasodilators were infused intravenously. Intravenous acetylcholine often led to an outpouring of previously retained CO_2, a decrease in arterial P_{CO_2}, an increase in arterial blood pH and Po_2, and a marked decrease in wasted ventilation. But in some babies, sustained pulmonary vasodilatation was obtained only by intravenous administration of sodium bicarbonate, thus confirming the findings of Liljestrand, and Enson and associates that acidosis is a potent pulmonary vasoconstrictor. The same combination of pulmonary ischemia, atelectasis, and hyaline membranes occurs in babies with respiratory distress syndrome and in dogs following experimental pulmonary artery occlusion.

No one knows yet whether the pulmonary ischemia in babies comes first and is causative or whether it comes later as a result of hypoventilation, hypoxia, and acidosis. And no one knows whether, if it comes first, it is due to episodes of fetal asphyxia or fetal hypotension or whether it is due to a failure of fetal pulmonary vessels to relax normally at birth. We still have to learn much about the mechanisms which, at the birth of a baby, simultaneously cause the pulmonary arterioles to dilate but the ductus arteriosus and the umbilical arteries to constrict. High oxygen concentrations are known to dilate pulmonary arterioles in the fetus and to constrict the ductus arteriosus and umbilical arteries even in vitro, but reflexes may also be involved.

Injection of nicotine (which stimulates both the aortic and carotid bodies) into the ascending aorta of man causes pulmonary vasoconstriction (Burgess, personal communication). In the dog, stimulation of only the aortic body leads to reflex pulmonary vasoconstriction; presumably lack of stimulation leads to pulmonary vasodilatation. It is of interest that although stimulation of either the carotid or the aortic bodies increases respiration, stimulation of the carotid body in the dog produces bradycardia and hypotension while similar stimulation of the aortic body produces tachycardia and hypertension (fig. 6). The aortic bodies of adult animals receive their blood supply from a branch of a coronary artery or of the aortic arch. In the fetus this vessel communicates with a small branch of the pulmonary artery; this vascular system is similar to the ductus arteriosus in that it connects the pulmonary artery and the aorta (though the diameter of the channel is far smaller) and it closes shortly after birth. We do not know whether this unusual blood supply has some significance in the reflex control of pulmonary vascular resistance or resistance to flow through the ductus arteriosus in the fetus.

We do not believe that there is a separate pulmonary body in the adult which receives blood from a branch of the pulmonary artery because we have never been able to find, beyond the newborn period, a patent artery to chemoreceptor tissue that arises from the pulmonary trunk or the right or left pulmonary arteries.

Hughes has presented anatomic evidence that the blood supply of the adult aortic body comes from the aorta in a roundabout way. Figure 7 (not shown) shows that a branch of the left coronary artery first becomes the vasa vasorum of the wall of the pulmonary artery; these recombine to form a

venous portal system which then breaks up into a second set of capillaries which supply the chemoreceptor cells that we call the aortic bodies. Can the composition of blood flowing through the pulmonary artery affect significantly the P_{o_2} and pH of blood flowing through these vasa vasorum in the wall of the pulmonary artery? Theoretically, it is possible if the diffusion path is very short and if the blood flow through the vasa vasorum is very slow; practically, it has not yet been possible to stimulate these chemoreceptors by changing the chemical composition of pulmonary arterial blood in intact animal.

Filtration

The pulmonary circulation, located as it is between the mixed venous blood and the systemic circulation, serves the important function of retaining fine particles present in mixed venous blood and preventing these from entering the systemic circulation and lodging in the end-arteries in other, potentially more troublesome, sites such as the coronary or cerebral circulation. There are many more pulmonary capillaries than are needed for effective gas exchange in resting man and some of these can

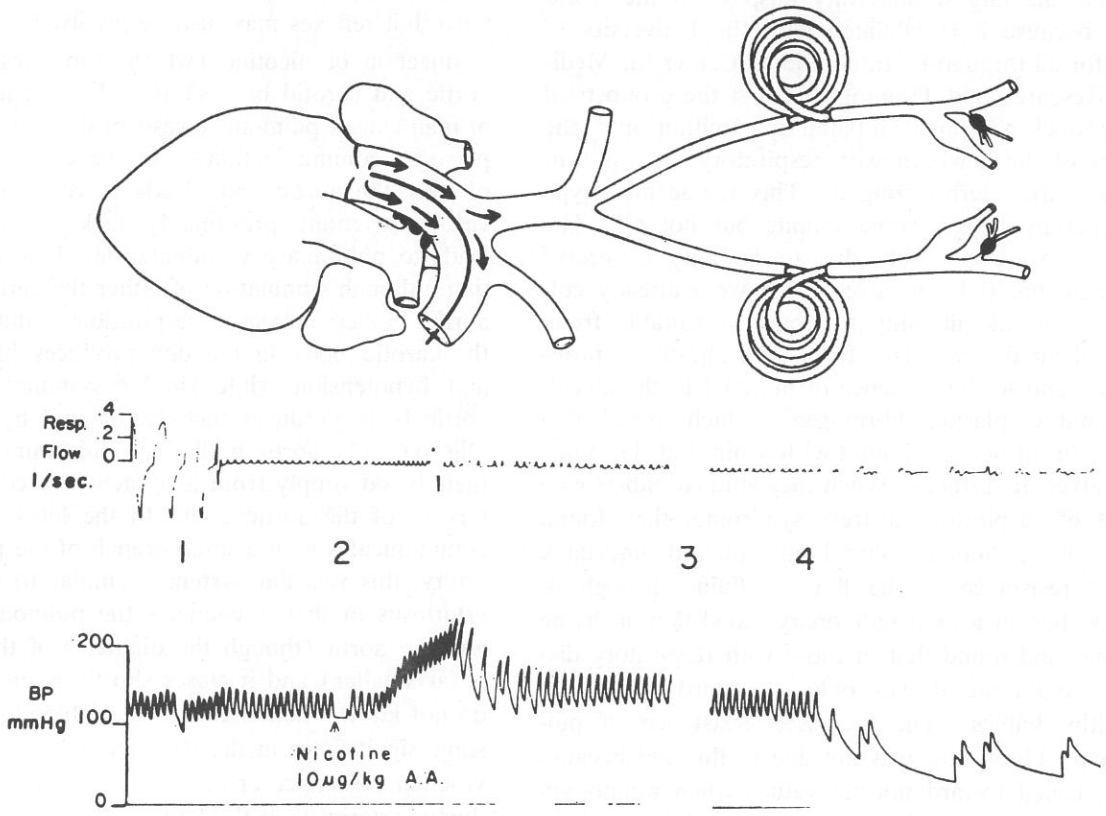

Figure 6

Temporal separation of aortic and carotid body stimulation. Above: Nicotine injected through a catheter placed in the aorta just beyond the aortic valves reaches the aortic bodies within 1 sec, but because it must pass through long delay paths (coil made of plastic tubing) inserted in the common carotids, does not reach the carotid bodies until 75 sec later. Below: Nicotine injected at 2 stimulates aortic bodies and causes tachycardia and hypertension; later (at 4) it reaches carotid bodies and causes bradycardia and hypotension. A neuromuscular blocking agent (succinylcholine) was injected at 1 to produce apnea and eliminate any effects of hyperventilation. Top tracing is respiratory air flow; bottom tracing is blood pressure on the cardiac side of the delay coils. A portion of the record was deleted at 3 to save space. (From Comroe, J.H., Jr., and Mortimer, L.: J. Pharmacol Exp Therap 146: 33, 1964.)

be sacrificed to protect other vascular beds; one lung and some of the other lung can be removed without producing anoxemia. It is now possible to estimate the size of the functioning pulmonary capillary bed by special tests that measure uptake of carbon monoxide at normal, high, and low oxygen tensions in inspired gas; if there is no primary alveolar disease, low carbon monoxide uptake means that there are fewer blood-filled alveolar capillaries in contact with ventilated alveoli (fig. 8). Recently, Gold and McCormack (personal communication) have measured pulmonary capillary blood volume in 12 patients before and 1 hour after injecting radioactive iodinated macro-aggregated serum albumin into an antecubital vein for the purpose of diagnostic lung scanning, as proposed by Wagner and associates. This test depends upon the plugging of some of the previously open pulmonary vessels by the macro-aggregates of albumin. The maximal amount of albumin injected was 1 mg; assuming that the average diameter of aggregates was 30 microns, the maximal number of emboli would be 70,000, enough to occlude about 5% of the precapillary vessels in the lung, if each entered a different vessel. As one might predict, the injection of these aggregates did not lead to measurable change in the uptake of carbon monoxide in any of the patients. However, in another group of patients, Gold and associates injected 20 ml of iodized oil (Ethiodol) into the dorsal pedal lymphatic vessels for diagnostic lymphangiography. This material eventually enters the venous blood and goes to the pulmonary circulation where the oil micro-emboli lodge in the pulmonary capillaries. Assuming that the average diameter of the Ethiodol droplets is 10 microns, 20 ml would produce 40 billion emboli—more than enough to block every pulmonary capillary. Gold and his associates found that the uptake of carbon monoxide diminished after the injection of Ethiodol; on the average, the pulmonary diffusing capacity decreased by 32% of control values and pulmonary capillary blood volume by 42% of the initial figure. Yet at this time these patients had no symptoms of breathlessness* and no changes from control values in lung volumes or arterial blood gas tensions.

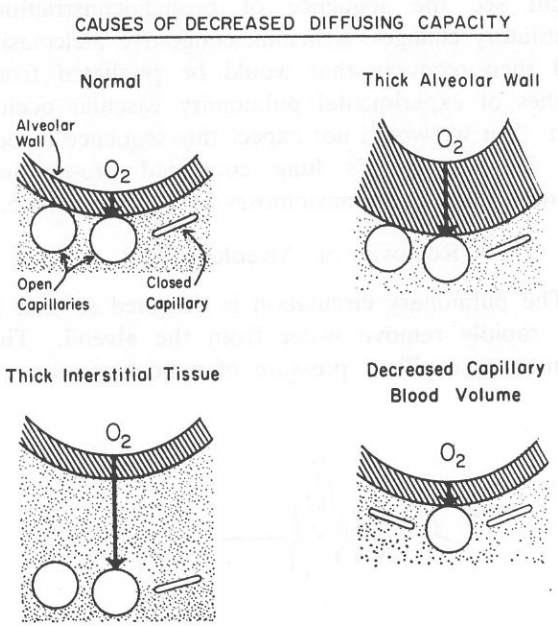

Figure 8

Causes of decreased diffusing capacity of the lung. Diffusion may be impaired because of a longer path between O_2 in the alveolar gas and pulmonary capillary blood (thick alveolar wall or thick interstitial tissue) or because of fewer blood-filled capillaries.

Of great interest is the fact that the diffusing capacity for carbon monoxide and pulmonary capillary blood volume returned to control values within 4 days. Obviously the pulmonary circulation possesses mechanisms for passing or disposing of macro- or micro-emboli and reestablishing the full number of open capillaries. These mechanisms deserve more study because it is likely that mixed venous blood often contains micro-emboli of tissue cells, fat globules, agglutinated red blood cells, sickle cells, while blood cells, platelets, parasites that occur normally, follow minor trauma, or occur in disease.†

Nadel and associates (personal communication) have recently studied a group of patients whose main pulmonary abnormalities were a decrease in carbon monoxide (presumably owing to obstruction of small pulmonary vessels) and an increased pulmonary compliance at all lung volumes. Because such a change in compliance has been reported previously only in patients with emphysema, they wondered whether prolonged block of capillaries (in such a way that they can be supplied neither by pulmonary nor by bronchial arterioles) precedes and causes loss of alveolar septal tissue. If so, the mechanism for opening plugged capillaries must be inoperative in these patients. This means that the factors which inhibit the normal scavenging of emboli also deserve study.

* Lymphangiography is a potentially dangerous test in patients who have pre-existing disease of the pulmonary circulation and it can be fatal; it is wise, when possible, to measure pulmonary diffusing capacity or pulmonary capillary blood volume before injecting Ethiodol.

† In 61 consecutive autopsies at the Beth Israel Hospital in Boston, Freiman and his associates found evidence of antemortem thrombi in 64%; it seems that large or small thrombi or emboli can be found in most older patients if a proper search is made for them.

I have labeled the filtering of particles from the mixed venous blood as a *function* of the pulmonary circulation—made possible by the large reserve in pulmonary vascular bed and the apparent harmlessness of some emboli. We have noted that block of a small percentage of precapillary vessels with macro-aggregates of albumin or of a large percentage of the capillaries with Ethiodol causes few if any measurable changes in respiration or systemic circulation. Yet sometimes, pulmonary emboli cause dysfunction and indeed can be fatal. The events occurring after pulmonary emboli are not necessarily related to the fraction of the vascular bed that is occluded. Block of one pulmonary artery by inflating a balloon at the tip of a catheter causes no symptoms and no important disturbances in ventilation or in the systemic circulation if the other lung is normal. But certain types of pulmonary emboli can cause reflex rapid and shallow breathing, constriction of alveolar ducts owing to release of histamine from mast cells, constriction of bronchioles owing to liberation of serotonin from blood clots, or systemic effects. Further, there is a well-defined pulmonary chemoreflex in some animals which, when stimulated by body constituents such as serotonin or adenosine triphosphate, can cause marked systemic hypotension, bradycardia and apnea. And strangely enough, some mechano-receptors in the lungs can be stimulated by certain chemical substances when these are injected into the pulmonary artery.

Much more remains to be learned about why some micro-emboli do and some do not cause effects in addition to local mechanical circulatory obstruction. Is the clue in their physical or chemical nature, in the point of their impaction, or in secondary chemical changes that occur locally after impaction? Even with more animal experimentation, there still will be the problem of species difference.

Figure 9 shows that serotonin injected into the pulmonary artery of a cat produces apnea—hypotension—bradycardia (from activation of the pulmonary chemoreflex) and into a dog produces hyperpnea—hypertension—tachycardia (from stimulation of the aortic and carotid bodies); in man, it produces variable changes.

The variability of the clinical and laboratory manifestations of pulmonary embolism in man have long been puzzling and have led to controversy. Some radiologists believe that the typical roentgenogram of the chest after pulmonary embolism shows an ischemic lung. Others have stated that the typical film shows sharply demarcated or wedge-shaped densities (infarcts), often associated with pleural effusion. Some radiologists who have reported these densities have seen them in the first 24 hours after the onset of symptoms, but others not until several days have passed. Clinicians have been puzzled by the fact that one patient can have occlusion of the right or left pulmonary artery with no effects but another may have occlusion of finer vessels and be seriously ill with dyspnea, substernal oppression, cough, hemoptysis, or shock. If we know the precise moment of impaction of an embolus in man (rather than the moment at which symptoms occur), we might see the sequence of bronchoconstriction, ventilatory changes, ischemia, congestive atelectasis, and then recovery that would be predicted from studies of experimental pulmonary vascular occlusion. But we would not expect this sequence to occur if the patient's lung contained pre-existing bronchopulmonary anastomoses of any magnitude.

Removal of Alveolar Fluid

The pulmonary circulation is designed so that it can rapidly remove water from the alveoli. The pulmonary capillary pressure of a healthy man (8

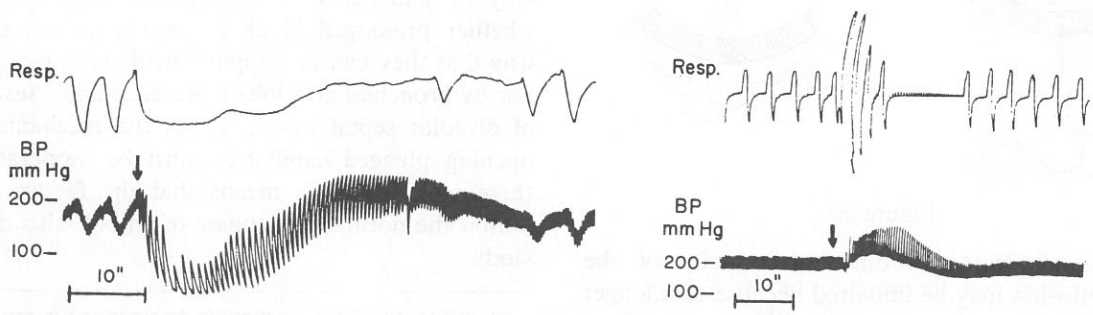

Figure 9

Effects of serotonin on respiration and blood pressure in the cat (left) and dog (right). Serotonin injected at arrows.

to 10 mm Hg), which tends to filter fluid from the blood to the alveoli, is normally far less than the colloidal osmotic pressure of the plasma proteins (25 to 30 mm Hg), which tends to pull alveolar fluid into the blood. This imbalance prevents transudation of fluid from blood to alveoli and hastens the reabsorption of alveolar fluid into blood. When tagged small molecules are dissolved in water and introduced into the alveoli, either by injection through a catheter or by inhalation as an aerosol, they enter the circulation almost as rapidly and completely as would an intravenous injection. This is why administration of procaine or isoproterenol into the lower airways can be hazardous.

It is widely believed that large molecules such as the plasma proteins leave alveoli slowly and only through lymphatic channels. Recently, it has been shown by Schultz and his co-workers that labeled proteins placed in alveoli enter the pulmonary circulation of perfused, isolated lungs. The particles could not have reached there through the usual lymphatic channels draining into the jugular veins and must have entered the pulmonary capillaries directly. This has been confirmed by Lee in our Institute (personal communication). The mechanism of the uptake of large molecules by pulmonary capillaries requires further study.

Comment

In concluding, I have discussed the major known functions of the pulmonary circulation. I predict that important new functions will be uncovered in the future. The pancreas has an exocrine function (long known) and an endocrine function, discovered many years later; the kidney has a filtration-reabsorption function (long known) and an endocrine function (formation of renin and hematopoietin) discovered much later. We may find unsuspected functions of the lung and the pulmonary circulation. Why is the lung rich in histamine, heparin, adenosine deaminase, and in certain proteolytic enzymes? Why are leukocytes, separated briefly from blood and then reinjected, trapped preferentially in the pulmonary circulation? Why do certain bacteria, given intravenously, stay in fine pulmonary vessels although they are small enough to pass through any capillary bed? Why do certain diseases of the lung lead to inappropriate secretion of antidiuretic hormone? Why is bronchial carcinoma often associated with clubbing of the fingers although there is no arterial hypoxemia? The answers to these questions will be interesting; I hope that you will find them.

(The references may be seen in the original article.)

MANAGEMENT OF LOCAL REACTIONS TO DUCK EMBRYO RABIES VACCINE*

Surgeon Comments (12): 2-3, December 1965.

With the commercial availability of duck embryo rabies vaccine in 1957 the grave danger of central nervous system complications associated with administration of rabbit brain vaccine was thought to be ended. This achievement of safety has been confirmed by the paucity of cases of central nervous system disease attributed to the new vaccine,[1, 2] but another type of hypersensitivity reaction has continued to appear with troubling frequency. It should not be surprising that repeated injections containing egg protein would induce local and even systemic allergic reactions. Indeed, such reactions have been a significant factor in preventing a large number of patients from completing the course of vaccination currently recommended by the World Health Organization.

Local reactions to duck embryo vaccine have occurred in one-quarter to one-half of patients,[2-5] usually consisting of pain, redness, and induration, occasionally with regional lymphadenopathy. Systemic reactions, such as urticaria, chills, fever, malaise and palpitation, are quite uncommon. In spite of the fact that such reactions are no more frequent than they were with rabbit brain vaccine, and may even be less severe,[6] they are probably the current major cause of uncompleted vaccination series. The following case report and comments are presented for the purpose of aiding in the management of such patients when these reactions appear.

Case Report:

A three year old girl sustained a minor bite on the hand by a cat which had unprovokedly bitten

* Submitted by CAPT Richard P. Lipman MC USA, US Army Hospital, Heidelberg, Germany, and presented at the USAFE Medical-Surgical Conference, 6-7-8 October 1965.

six other people. The animal escaped and rabies was suspected in view of the animal's unusual behavior. Duck embyro rabies vaccine was administered to the child in a dose of 1 cc. subcutaneously daily. The sixth and seventh doses were accompanied by intense local itching with extensive redness and swelling, the fever up to 101°. There was no previous history or family history of allergy.

It was decided to continue the course of vaccination while attempting to suppress the allergic reaction. Use of adrenal corticosteroids was discarded because of their unpredictable effect on immunization, although 20 mgm. of Prednisone was given orally 24 hours before the eighth dose of vaccine. She was begun on Diphenhydramine hydrochloride (Benadryl) 25 mgm. orally every six hours and Epinephrine in oil 1:500 0.2 cc I.M. every eight hours, and the vaccination was continued.

The first two subsequent injections produced minor erythema and induration, but the third was accompanied by intense redness and temperature of 100°. Thereafter there was no further fever and locally only minimal induration and faint erythema of about 4 cm. around each new injection site. Twenty-four hours after the 14th and last injection, Diphenhydramine and Epinephrine were discontinued and nine hours later the patient developed a diffuse red facila blush with multiple red papules as well as intense erythema of the last injection site. Her medications were resumed and the blush disappeared in 18 hours, the local erythema persisting about 48 hours. The medications were then discontinued with no new phenomena noted.

Of the six other people bitten by the cat, five underwent vaccination. Two developed minor local erythema and induration of the fifth through eighth days. One other had these findings to a marked degree on the seventh and eighth days, whereupon the vaccination was discontinued.

Discussion:

There is evidence to suggest that the local allergic reactions to duck embryo rabies vaccine are worse in the middle third of the course, thereafter tending to subside.[4] Given this finding it seems reasonable to try to complete the vaccination series, particularly when the original decision has been made by a Rabies Board which has weighed the risks to the patient from rabies against the high incidence of allergic reactions.

Attempts to control more serious local and mild systemic reactions with pituitary and adrenal corticosteroids at first may appear to be worthwhile, but the effect of such compounds on the body's immune response to both vaccine and the rabies infection is unpredictable at present. That a subclinical temporary rabies carrier state may exist and even be activated into clinical disease has been suggested by the following study. A group of guinea pigs was given lethal doses of rabies virus. Twelve survived, apparently unharmed. Of these survivors, three developed clinical rabies and died when given a course of ACTH 7½ months after the original infection.[7] Rabies virus was cultured from one of these animals. Also, in a human treated with rabbit brain vaccine, cortisone, and ACTH, failure of neutralizing rabies antibodies to develop has been demonstrated.[8] Further investigation with rabbits treated with cortisone by the same group showed no significant antibody production to the rabies vaccine, and there was moderate impairment with ACTH. Until further information is available, it would thus seem hazardous to attempt control of mild and moderate allergic rabies vaccination phenomena with such compounds.

The use of antihistamines and sympathomimetics, especially long-acting epinephrine, is well-established in the control of allergic reactions, and presents little danger to the patient. Although the brief administration of Prednisone to the above patient makes it difficult to draw conclusions from the subsequent course, it is clear that the withdrawal of an antihistamine and sympathomimetic was followed by a systemic and markedly intensified local reaction. This reaction occurred at least 12 hours later than would have been expected if it were caused directly by the last vaccine injection, and cleared fairly rapidly after the medications were resumed. This strongly suggests that the medications were inhibiting a more severe allergic reaction. It may therefore be possible to complete a large number of heretofore discontinued rabies vaccinations with moderate allergic reactions by the use of such drugs for long periods.

Finally, the technique of administration should be considered. One series has demonstrated more intense local reactions with intradermal injection even when 0.2 cc. was given rather than 1 cc subcutaneously.[5] Perhaps even a minute amount of vaccine adhering to the outside of the needle can result in an "intradermal" injection producing an intensified local allergic reaction even when the main bolus is injected subcutaneously. Certainly, following the intramuscular injection of a few antibiotics many physicians have noted a reduction in severity of local subcutaneous induration when a fresh needle

replaced the one used to draw up the material. It would be interesting to compare the vaccination reactions using a double needle technique and the usual method in two large groups.

Summary:

A discussion of the incidence and manifestations of local and systemic reactions of duck embryo rabies vaccine is presented. Three methods for control of these reactions are considered. The possibly utilization and effectiveness of antihistamines and long-acting sympathomimetics is emphasized. The potential hazards of pituitary and adrenal corticosteroids are reviewed; and an alteration in injection technique is suggested.

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GEOGRAPHICAL DISTRIBUTION OF CANCER IN EAST AFRICA: A NEW CLINICOPATHOLOGICAL APPROACH

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BRIT MED J 2: 719-722, SEPT 25, 1965.

Geographical pathology is the study of disease-incidence rates in different geographical areas. Comparison may be made between widely separated areas with considerable geographical and economic differences, such as Great Britain and East Africa, or between more closely related countries, such as Uganda and Nigeria, or between different areas in the same country. It is this latter approach that we wish to stress in this article.

In most technologically advanced countries with mobile populations the majority of people live under very similar circumstances apart from specific hazards associated with special industries and individual customs. By contrast, in East Africa there are still many groups of people living in circumscribed communities in different geographical circumstances and exposed to widely varying nutritional, social, economic, and other environmental factors. These groups do not correspond to political boundaries, and from the standpoint of disease Southern Sudan can be regarded as an extension of Northern Uganda; South-west Uganda is part of the mountainous area containing Kivu, Rwanda, and Burundi (Fig. 1); and the coastal plains of Kenya and Tanzania have many more factors in common with each other than with their own inland areas. Similarly, on a tribal basis the Karamajong of Uganda, the Suk of Kenya, and the Masai of Kenya and Tanzania have many more factors in common with each other than with other tribes in the same territory. The Bakiga people of Uganda in turn share more environmental factors with the Banyarwanda than they do with other Uganda tribes. In the study of geographical factors in any disease process the study of intraterritorial differences must go hand in hand with the interterritorial and international studies (Burkitt, Nelson, and Williams, 1963).

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** Medical Research Council External Scientific Staff.

Methods

The pioneer work of Davies, Wilson, and Knowelden (1958, 1962) has already demonstrated significant differences between the pattern of cancer in the Kyadondo area of Uganda and most Western countries. It has been shown, however, that some tumours do not have a uniform incidence in East Africa. Early in the epidemiological studies on African lymphoma it was observed that this tumour is virtually never seen in the densely populated high area of South-west Uganda. Dodge, Linsell, and Davies (1963) have also shown marked differences between the incidence of cancer of the penis in Uganda and in Kenya, and related this to differences in the customs of circumcision between Ugandan and Kenyan tribes.

These facts led us to wonder whether other tumours may show marked differences in incidence in East Africa and surrounding countries.

In 1963 we decided to start a new approach to the cancer situation to try to fill in some of the gaps in our knowledge of the cancer pattern in East Africa, particularly in Uganda.

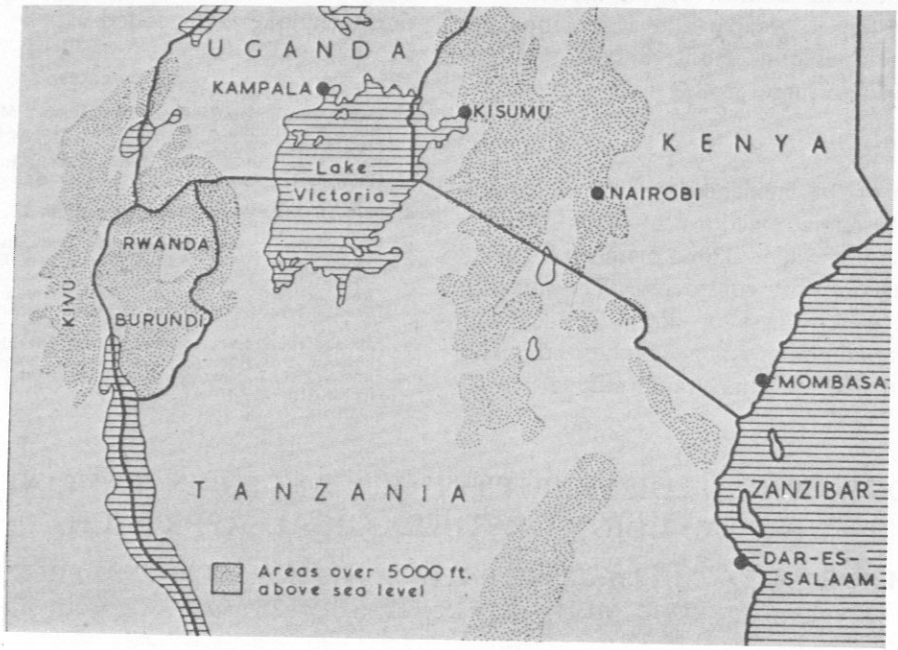

Fig. 1.—Map of East Africa showing main centres and high-altitude areas.

The first step was to open up the diagnostic histology service to all hospitals in Uganda, and to encourage biopsies, particularly of selected tumours. This was aided by the use of biopsy bottles containing neutral formalin prepackaged together with request forms requiring details of age, sex, tribe, and habitation, similar to those used by Davies et al. (1958) for the Kyadondo survey. As a result of this step the overall biopsy rate went up from 4,500 in 1962 to 6,900 in 1964. All histologically proved cases of cancer from Uganda are now registered, and 1,500 new cases were recorded in 1964. Fortunately, while valuable for research, this operation is still more valuable as a link between outlying doctors and the university centre, and is much appreciated for this reason as well as for the practical service offered.

The second step was to establish direct contact with the doctors in all the hospitals in Uganda, and in most of Kenya and Tanzania, to acquaint them with the scheme, to encourage biopsies, and particularly to obtain routine returns providing particulars of certain selected tumours. During these visits the opportunity was taken to probe into the experience of the local doctors, and to examine returns and operation records with a view to establishing some ideas of certain cancer frequencies. In East Africa there are a number of mission hospitals that have doctors who have served them for over 10 years and not a few for over 20 years. This staff continuity means not only that impressions of incidence have been formed over many years but also that an added interest in accurate records has in many instances led to careful recording of cancer and other figures and to the establishment of miniature cancer registries.

Several mission hospitals in East Africa have been keeping careful records of their cases of cancer, and these have provided valuable information. Thus Dr. Joe Taylor (1964), at the "Jungle Doctor" Hospital at Mvumi, in Tanzania, was able to compare experience at the hospital with the review of the Mengo Hospital experience recorded by Davies, Elmes, Hutt, Mtimavalye, Owor, and Shaper (1964).

Discussions with many clinicians and examination of existing records, during extensive travel, have led to the emergence of some cancer and other disease patterns throughout East Africa which supplement the more detailed and accurate results for Uganda recorded in the Cancer Registry. These are being followed up through the biopsy service and regular returns.

Results

In this paper we are concerned with outlining our general methods of geographical study in Africa and reporting some preliminary observations. The

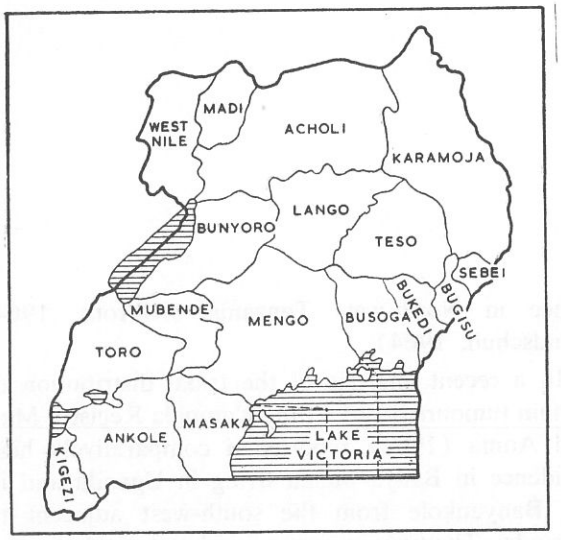

Fig. 2.—Map of Uganda showing districts.

latter can be divided into the factual information derived from the Cancer Registry for Uganda and the general impressions obtained from visits and postal communication with adjacent countries.

In the Table are shown the percentage incidences of selected tumours from different areas of Uganda (Fig. 2) for 1964, together with the number of cases and the total returns from the area. The regions chosen for camparison had all been visited by us before 1964, and biopsies had been encouraged and facilities made available. All the hospitals in each region were included in the scheme. The Table shows the fallacy of expressing returns for individual tumours from the whole country as a percentage incidence. Selection of the tumours for this preliminary report was based on the fact that they were easily diagnosed clinically and accessible to biopsy. Moreover, they were relatively common, and verbal reports had suggested different incidence rates in various areas of East Africa.

Cancer of the Penis

The lower incidence of this tumour throughout most of Kenya has been reported by Dodge et al. (1963). In contrast to Uganda the majority of tribes practice circumcision, and penile cancer is prevalent only in the western part of the country, chiefly among the uncircumcised Luo. These authors also noted considerable differences between uncircumcised Ugandan tribes, and these differences have been confirmed by Kyalwazi (1964). These reports are borne out by our returns for 1964, which show that cancer of the penis accounts for 17% and 20% respectively of all malignant tumours in Teso and Bunyoro, whereas in Lango and West Nile/Madi the figures are only 1.4% and 0.0% (see Table). We have discussed these differences with good clinicians who have spent several years in these areas, and the differences bear out their experience. As none of these tribes circumcise it is evident that secondary factors must be vital in the production of carcinoma; it is hard to believe that there were significant differences in social hygiene between these groups, and further studies will be necessary to elucidate factors such as infection (Ntuyabaliwe and Mluge, 1965).

There is no significant relation between the incidence of carcinoma of the penis and carcinoma of the cervix. For example, the Cancer Registry returns for 1964 show that, whereas in Lango there were nine cancers of the cervix to one of the penis, in Teso there nine cancers of the cervix to 16 of the penis. In Zanzibar (Chopra, 1964) cervical cancer is the most frequently observed cancer, though cancer of the penis is unknown.

Kaposi's Sarcoma

This tumour is relatively common throughout East Africa, accounting for about 4% of all malignant tumours. The cancer registry figures for 1964 suggest that the disease is more common in the west, particularly the north-western area of the West Nile and Madi, where it accounts for 18.2% of all registered tumours (see Table). This area abuts on to the North-east Congo, from where the highest incidence in Africa has been recorded (Oettlé, 1962). A high incidence of Kaposi's sarcoma has also been observed in Rwanda and in Eastern Kivu, both of which form part of the Western and South-western borders of Uganda (Gigasse, Clemmeson, and Maisin, 1962). This observation was recently confirmed by one of us (D.B.) during a visit to all Rwanda hospitals and the Central Laboratory at Butare.

In both Kenya and Tanzania Kaposi's sarcoma appears to be uncommon on the costal plains (Slavin, 1965). Zanzibar seems to be almost exempt, only one case having been recorded.

Squamous-cell Carcinoma in Tropical Ulcer Scars

By contrast with Kaposi's sarcoma the incidence of malignant change in tropical ulcer scars appears to be very low in the north-west (3.6%) and to have a focus of very high incidence in Lango (21.0% of all tumours) (see Table). Ntuyabaliwe and Mluge (1965) and Shepherd (1965) have drawn attention to the low incidence in people of the Baganda tribe.

Burkitt's Tumour

Over 500 cases of this tumour have now been recorded in Uganda. Less than 4% have come from the south-west, most of which is at an altitude of over 4,500 ft. (1,370 metres). Over 20% of the population of Uganda live in this region.

Breast Cancer

No significant differences in incidence have been observed.

Hepatoma

The tumour is common throughout the area under consideration, and an attempt is being made to obtain better returns from up-country by the encouragement of liver biopsy, both in life and at necropsy. Eighty-one cases were registered in Uganda in 1964, forming 5.5% of all malignant tumours. The only unusual finding was that six cases were recorded in Karamoja, which is thinly populated by nomadic herdsmen. In relation to the overall returns from this area it is a very high incidence. In view of the suggested relationship between primary liver cancer and Aspergillus flavus it is interesting to note that these people live mainly on blood and milk, although they do also store grain crops.

Preliminary impressions outside Uganda suggest that the tumour has a very high incidence throughout the central plain of Tanzania, where in several hospitals it was said to be the most frequently observed cancer.

Cancer of the Stomach

Davies (1959) has pointed out the low incidence of gastric cancer in the Kyadondo area of Buganda, and most figures from other parts of Africa confirm this. However, throughout much of Rwanda the condition is thought by many experienced doctors to be one of the commonest neoplasms. In Eastern Kivu, which is topographically an extension of the Rwanda hills into the Congo, Ceuterick (1960) and Gigasse et al. (1962) have produced convincing figures that suggest a very high focal incidence in these areas. There also appears to be a high incidence in North-west Tanzania (Nillroth, 1964; Bundschuh, 1964).

In a recent analysis of the tribal distribution of certain tumours based on the Kampala Registry Mati and Auma (1964) reported a comparatively high incidence in Banyarwanda living in Uganda and in the Banyankole from the south-west adjacent to Rwanda. The tumour appears to be particularly rare in Northern Uganda. Williams (1965) has seen only one case in a series of 222 malignant tumours recorded in Kuluva Mission Hospital, and De Souza (1965) has not seen a single case during the two and a half years as surgeon in the busiest surgical unit in the northern region.

Cancer of the Oesophagus

Within East Africa great variations in incidence of oesophageal cancer are observed. There appear to be two areas of unusually high incidence, in contrast with other areas where the disease is not recognized.

Several workers, and in particular Miller (1964), Nevill (1964), and Clifford (1964), have drawn attention to the local concentration of this disease around Kisumu on the north-east shore of Lake Victoria. Ahmed (1965) has studied this problem in detail. He is recording approximately 40 cases a year with histological confirmation at Kisumu Hospital. This is more than double the total cases recorded at Mulago Hospital in Uganda, which contains four times as many beds and is the referral centre for all Uganda. Three mission hospitals within 50 miles (80 km.) of Kisumu estimate that oesophageal cancer is their most frequent observed neoplasm. At the next provincial hospital, less than 100 miles (160 km.) to the east, da Cunha (1965) reports that most of the cases referred to him have come from the Kisumu area.

A second area of high concentration is apparent in the vicinity of Mount Kenya. The provincial hospital situated at Nyeri to the west of the mountain received referred cases from all this area and records an estimated 10-15 oesophageal cancers annually. There is some evidence suggesting that the

majority of these patients come from the east of the mountain, where two mission hospitals with 100 and 150 beds respectively see an estimated 10-15 cases a year each.

In contrast to these two areas of high incidence of oesophageal cancer no doctor throughout Rwanda could remember having seen a single case, and Williams (1965) has recorded no case in his 24 years in Northern Uganda. Gigasse et al. (1962) recorded the apparent absence of oesophageal cancer in Eastern Kivu, which is topographically only an extension of Rwanda. The tumour also appears to be very rare in the areas of South-west Uganda and Western Tanzania adjacent to and topographically identical with Rwanda.

Discussion

It is evident that in East Africa significant variations of incidence in certain cancers can be observed between areas closely related geographically. The clarification and confirmation of these emerging patterns should provide an opportunity to search for environmental factors common to areas showing a similar incidence or differing between areas of high and low incidence.

Much information has already been obtained by analysis of central laboratory histological records. In the three East African countries all histology has been done for many years in laboratories in the capital cities. Figures for cancer incidence based on these central records, while giving a general pattern, may be very misleading if they are not analyzed on a local geographical basis. Furthermore, the returns from different parts of the country show a great variation. The most accurate and valuable figures so far obtainable have been derived from Kampala Cancer Registry survey of Kyadondo country (Davies et al., 1958, 1962). It is evident, however, that while surveys of very localized areas such as Kyadondo will produce more accurate figures they will miss the variability that we know exists even in such a small area of Uganda.

It is considered essential that a combined clinicopathological approach be made to this problem. Active co-operation from clinicians is an essential preliminary to the provision of biopsy material, and this can best be achieved after initial personal contacts. On the other hand, only histological confirmation can provide the accuracy of diagnosis without which purely clinical diagnosis can always be open to doubt. Initially, investigations must be limited to a selected small group of tumours such as those discussed in this paper.

It is as true in medicine as elsewhere that you see what you look for. The absence of a condition in an area, which may be more significant than its high incidence, can be determined only if observers are specifically looking for it. An active search can be maintained by any one individual for only a limited number of conditions.

Although this paper has been limited to the geographical study of cancer, this combined clinicopathological approach has gleaned information which indicates that several non-neoplastic conditions exhibit even more striking patterns of distribution which warrant further study.

The statistical purist may well comment that figures for cancer incidence based on such evidence are useless. We do not believe this to be true, and we feel that in an area such as this every factual piece of knowledge is of value.

Summary

Carcinoma of the penis, Kaposi's sarcoma, squamouscell carcinoma of the skin, oesophageal cancer, and gastric carcinoma have a variable incidence in different parts of Uganda and probably in other areas of East Africa. General statements about cancer in Africans should therefore be accepted with reserve. More accurate figures are needed before studies on aetiology can be started. These figures may be attained by a combined approach on the part of the clinician and pathologist. Personal contact is an essential feature of such a programme.

Our thanks are due first to the Ministries of Health of Uganda, Kenya, Tanzania, and Rwanda for their permission to make these safaris and to visit Government hospitals. We would also like to thank all the doctors in both Government and Mission hospitals throughout East Africa for giving up valuable time to discuss their work. Finally, we would like to thank all our colleagues in the New Mulago Hospital and the Makerere University College Medical School for their help, advice, and co-operation. We would also like to acknowledge our debt to Professor J. N. P. Davies, who initiated this type work in East Africa.

Financial support for these activities has been provided by the Medical Research Council and the British Empire Cancer Campaign.

Figs. 1 and 2 are acknowledged to the Department of Medical Illustration, Makerere University College Medical School.

Our thanks are due to Mrs. Barbara Wright, cancer registrar, for the figures shown in the Table.

(The references may be seen in the original article.)

FROM THE NOTE BOOK

ACUTE NON-ALLERGIC REACTIONS DURING TREATMENT WITH DEPOT-PENICILLIN

A description is given of acute non-allergic reactions following i.m. administration of procaine-free and of procaine-containing preparations of depot-penicillin having crystals of a certain size-range (30-60 μ). The patients present unpleasant, mainly central symptoms with acoustic and optic sensations, but all these symptoms gradually disappear again, and a fatal outcome has never been observed. These reactions are seen once in approximately 300-400 injections of these preparations. Evidently, they are manifestations of crystal embolism as the result of accidental penetration of the injected material into the blood stream; injection pressure and tissue lesions from earlier injections appear to play a part in this connection. It is assumed that in these accidents the size of the crystals determines the severity of the symptoms, and that the duration of the reaction depends on the solubility of the crystals in the blood. After the crystals in clemizol-penicillin G had been reduced in size to less than 20 μ, in more than 1,200 injections only one reaction of the type described was observed, and that was greatly attenuated.—Arthritis and Rheumatic Diseases Abstracts 2(4): 187, Abs No. 1007, Feb 1966.

11 MAJOR DRUGS—THERAPEUTIC ADVANCES OF 1965 CITED BY MEDICAL AUTHORITIES

Eleven drugs and vaccines have been designated as 1965's "important advances in drug therapy" in a poll of leading medical researchers and clinicians.

The eleven products improve treatment for staph infections, tetanus, certain types of cancer, fungus infections, rheumatoid arthritis, severe itching, rabies and smallpox.

Also, electronic cardiac pacemakers were called a "breakthrough" for the treatment of several types of heart disease.

The poll was conducted by The Medical Letter, the fortnightly newsletter which critically evaluates new drugs for the medical and allied professions. The medical authorities participating in the poll are engaged in all branches of medicine at hospitals, medical schools and research centers throughout the United States. They regularly help to assess drugs for the publication.

Results of the poll are contained in a foreword to the newly published bound volume of 1965 issues.

Named as the one "breakthrough" product were the electronic cardiac pacemakers. These are small devices which by electrical stimulation cause a heart that has stopped to start and continue to beat.

"These devices, which have been greatly improved since their introduction several years ago, are life-saving in many patients with heart block associated with Stokes-Adams syndrome, congestive failure and coronary or renal insufficiency," The Medical Letter said.

Of the 65 drugs and therapeutics evaluated by The Medical Letter during 1965, the panel named the following eleven drugs as "useful additions to therapeutic practice":

1. Cephalothin: a semi-synthetic antibiotic which has proven its usefulness in severe infections which are normally treated with penicillin, when the patient is hypersensitive to penicillin.

2. and 3. Cloxacillin and lincomycin: two other antibiotics which the panel found to be effective against staph infections resistant to other antimicrobial agents. Cloxacillin is a semi-synthetic penicillin; lincomycin is similar in the range of its activity to erythromycin, but it is useful against some strains of staphylococci which are resistant to erythromycin.

4. Tolnaftate: a new antifungal agent which is effective against a wide variety of pathogenic fungi causing superficial skin infections.

5. Dactinomycin: an antibiotic which has little antimicrobial activity but which has produced marked improvement in certain forms of cancer. Because it slows the growth of normal as well as malignant cells, the drug's use must be carefully supervised to prevent damage to normal tissues, especially bone marrow and the lining of the digestive tract.

6. Indomethacin: a new anti-rheumatic drug which has proven effective in many patients with moderately severe rheumatoid arthritis, though it appears to have little value for patients with severe cases of the disease. The panel said that although it is not free of side effects, "it may prove to be

the safest available anti-arthritic agent other than aspirin."

7. Cholestyramine: a drug that relieves the itching which accompanies jaundice resulting from certain liver ailments.

8. Triamterene: a new diuretic which has the advantage of not causing loss of potassium from the body. It is useful chiefly in combination with other diuretic drugs.

9. Tetanus immune globulin: this effective tetanus antitoxin made from human serum is an important development because it does not cause serum sickness or other reactions frequently brought on by equine or bovine antitoxin.

10. Duck-embryo rabies vaccine: this vaccine for immunization against rabies reduces the risk of encephalitis, or brain damage, which often follows the use of the widely used nerve-tissue vaccine.

11. Vaccinia immune globulin: this vaccine can provide effective protection for persons who have been exposed to smallpox and who are not protected by vaccination. It has also proven valuable in the treatment of smallpox and the complications of vaccination.

Four drugs, which are said to have been heavily promoted, received lowest ranking in the poll. They were: oxazepam (Serax), tybamate (Solacen), chlorphentermine (Pre-Sate) and benzphetamine (Didrex).—Norman A. Schorr & Co., 605 Third Avenue, New York, N.Y.

DENTAL SECTION

A REVIEW OF CAUSES OF FAULTY ROENTGENOGRAMS

CAPT C. R. Parks DC USN, Head, Oral Diagnosis Dept, U.S. Naval Dental School, NNMC, Bethesda Md.

Roentgenography is one of the most important aids to diagnosis we have; and, as with all other aspects of dentistry, good results depend on paying attention to details. Poor quality roentgenograms fail to provide all the information that can be obtained from this source. Too often the first reaction to poor quality is to blame the x-ray film. In some cases this is justified, but very often the unit itself, the roentgenographic technique, the processing of films, or all of these, are to blame. The purpose of this paper is to review the most common faults and what can be done to correct them.

A. Technique and X-ray Units.

1. Variation in target (focal spot of the target) -film distance. The end of the cylinder (long cone) must always touch the skin. Otherwise, there will be a variation in the film density due to the variation in the target-film distance. The intensity of the radiation varies inversely as the square of the distance from its source. Therefore, if the target-film distance is doubled, the exposure time must be quadrupled, all other factors remaining the same. For example, if an exposure time of 0.5 seconds is being used with the recommended 16-inch target-film distance and the distance is increased to 18 inches, the time will have to be increased to more than 0.6 seconds.

2. Reverse placement of film. This is not a common fault but will obviously result in a light film because of the lead backing in the film pack. Lead is one of the best shielding materials and will effectively stop many of the rays.

3. Blurred image. The most common causes of this fault are (a) movement of the patient, the tube-head, or the film; (b) running and swelling of the gelatin on the film due to excessive heat; and (c) two exposures on the same film. Corrections are self-evident.

4. Fluctuation in line voltage. Most, if not all, of the x-ray units in use in the Navy today have a stabilizer in the circuit to compensate for this possibility. However, with excessive fluctuation of current the stabilizer may not be able to compensate sufficiently. This is most likely to occur when a ship receives its electrical supply from the pier, or when the electrical source is shared with a diathermy machine, medical x-ray units, or other electrical equipment.

5. Filtration. X-ray units operating up to 70 kvp. should have a total filtration equivalent to 2.0 mm. of aluminum. Those operating above this figure should have 2.5 mm. total filtration. Total filtration is the sum of the inherent filtration (that filtration built into the machine) plus the added filtration

(that which is created by aluminum disks placed in the useful beam). The optimum total filtration is very important for the safety of the patient. However, too much filtration will result in roentgenograms that are too dense.

6. Collimation. The useful beam must be collimated to a maximum diameter of 3 inches at the end of the cylinder (cone). This is done with the lead diaphragm placed in the path of the beam, either in the base of the cylinder or in the tubehead. Any appreciable increase in the target-film distance requires a new diaphragm with a smaller aperture to collimate the beam correctly. If this is not done, the patient is subjected to needless radiation and there is increased chance for film fog due to secondary radiation from peripheral tissues.

7. Timer. With the use of the "D" speed (ultraspeed) film required in the long-cone technique, an electronic timer is a virtual necessity. The mechanical timers are not accurate below 1 second. Any attempt to use them below that time will result in completely unpredictable roentgenographic results. The contacts in the timer button should be checked periodically to ensure their proper functioning, and therefore accurate exposure.

B. Film.

1. Storage. X-ray film should be stored, ideally, in a cool room (50° to 70° F.) and at a relative humidity of 40% to 60%. The film should be protected from any radiation source, and should not be stored near a heat source such as a radiator or steam pipes, or where vapors such as formalin, hydrogen sulfide, hydrogen peroxide, or ammonia can fog it.

2. Age. Outdated film should not be used.

3. Condition. Obviously, film could become fogged or deteriorated before it is received by the activity that is to use it. The following simple test for inherent film fog can be done in the darkroom. Take a sample film directly from the package, unwrap it, and process it as though it were being exposed for diagnostic purposes. Unwrap a second film and place it directly in the *fixer* solution. Do this either in total darkness or with a proper safelight. The second film will be totally clear and the first should be clear. If the first film shows visible density, it has acquired fog and the rest of the package should not be used.

C. Film Processing.

The darkroom and the equipment therein are as important to the final product as the film itself or the roentgenographic technique. Unfortunately, this is one area that is often neglected.

1. Light leaks. To check the darkroom for light leaks, stand in the room for 10 minutes without any illumination, even from the safelight. Light leaks can be observed during this period as the eyes accommodate to the darkness. Another possible source of fogging from extraneous light is the glow from a cigarette, particularly with the extremely sensitive high-speed film now employed.

2. Safelight. The safelight should be a maximum of a 10- or 15- watt bulb behind an *intact* Wratten 6B filter. The filter must not have any cracks or chips that will allow light leaks. The safelight should be at least 4 feet from the working surface. *Safelight* test: (a) Expose a periapical film under the usual clinical procedure. (b) Unwrap the film in a totally dark darkroom. (c) Place the film on the working surface, and on the film's surface place a coin. (d) Turn on the safelight and leave the film on the working surface for a period of time equal to the average working time if two or three full-mouth series were being readied for processing; that is, if the first film unwrapped might be exposed to the safelight for 15 minutes, leave the test film on the working surface for that period. (e) Turn off the safelight, remove the coin, and process the film. If the outline of the coin is visible, the safelight illumination is excessive and should be reduced, or the filter is faulty and should be replaced.

3. Tanks. Metal tanks should be of stainless steel because it will not react with the processing reagents. The joints should be welded, smoothed, and polished. Tanks that show pitting or porosity should be replaced. Some metals will enter into a chemical reaction with the processing solution, causing deterioration of the solution and creating film fog.

4. Cleanliness of tanks. *Every* time solutions are changed, the tanks should be scrubbed with soap and water, then thoroughly rinsed. If the tanks are removable, they should be labeled so that there is no interchange between developing and fixing tanks. After rinsing, the *fixer* tank should be further rinsed with 10% acetic acid to neutralize any alkalinity remaining from the soap.

5. Tank covers. Tanks should always be covered when not in use and, again, stainless steel is the best material. Solutions, especially the developer, will deteriorate more rapidly through oxidation if not covered. This of course results in roentgenograms of poor quality. The covers should also be

prominently labeled so that there will be no interchange at any time.

6. Solutions. A good rule of thumb is that developing and fixing solutions should be changed every 3 weeks. This is variable depending on the workload. Solutions deteriorate mainly through use and oxidation. They will also be weakened by dilution if water is added to maintain the level of the solution. They should be stirred several times a day (a minimum of twice), preferably with a glass rod. Stirring rods should not be interchanged between tanks.

7. Time and Temperature. If the *full* developing time is used, the quality of the roentgenograms will be uniformly good, once the proper roentgenographic technique, including the correct exposure time for the film, is established and the temperature of the processing solutions is controlled. If these important factors are slighted, the quality will deteriorate.

The temperature of the solutions should be maintained at 68° to 70° F. for best results. At any activity, a refrigerated and thermostatically controlled processing unit is needed or desirable regardless of workload. The alternative is to use a mixing valve, properly installed and in good working order. However, the incoming cold water should never exceed 68° to 70° F. to be effective.

The temperature of the developer during use should never be allowed to fall below 55° F. Below this temperature the reducing agents form a cloudy precipitate that is very hard to redissolve, even when the solution is reheated. At developer temperatures above 75° F. chemical fog increases sharply. At lower temperatures the density of the image tends to decrease owing to retardation of development, even with a prolonged developing time. Below 60° F. hydroquinone (one of the chemicals of the developer that controls contrast) becomes inactive.

8. Rinsing and washing. In the processing procedure, films should be thoroughly rinsed between developing and fixing; and after being fixed for at least 20 minutes, they should be placed in circulating water for complete washing. Washing should continue at least 30 minutes to 1 hour. A properly fixed and washed roentgenogram will retain diagnostic value indefinitely; but when these procedures are done improperly, the roentgenogram will become stained and unusable either within a few days or as much as 2 or 3 years after processing.

9. Cleanliness. Throughout all aspects of film processing, the importance of cleanliness of equipment, working surfaces, and the darkroom cannot be overemphasized.

Conclusion

It must be constantly remembered that the film used with the extended cone technique is extremely sensitive to light, radiation, chemicals, and temperature. The manufacturer's directions are very important to best results and must be adhered to. If care is exercised throughout all steps of roentgenography and film processing, results will be of consistently high quality.

Editor's comment: The Inspector General, Dental, has observed that the darkroom light-leak is the most frequent reason for unsatisfactory dental roentgenograms.

PERSONNEL AND PROFESSIONAL NOTES

KNOW YOUR DENTAL CORPS

U.S. Naval Air Station, Atsugi, Japan,
U.S. Naval Security Group Activity,
Kamiseya, Japan.

The U.S. Naval Air Station, Atsugi, Japan is located in the rural Kanto Plains area on the island of Honshu about 25 miles southwest of Tokyo. Atsugi has a view of the majestic conical peak of Mount Fuji, rising 12,395 feet above sea level. The Naval Air Station has numerous facilities to fill the leisure hours of military personnel and dependents, including one of the finest golf courses in Japan.

The Dental Department has been in operation since 1950. Its spaces consist of six units for the practice of general dentistry, one for preventive dentistry, one prosthetic unit, one oral surgery unit, and one oral examination room as well as auxiliary spaces. The spaces are partially air conditioned.

There are twelve authorized military personnel on board, consisting of five dental officers and seven technicians, supplemented by four Japanese Nationals consisting of two dental operating room assistants, one oral hygienist, and one prosthetic laboratory technician. The clinic serves both military personnel and military dependents.

Nearby, and also in a rural part of Japan with a view of majestic Mount Fuji, is the Dental Department at U.S. Naval Security Group Activity, Kamiseya, Japan. This clinic consists of two dental operating rooms, a combination X-ray and preventive dentistry room, and auxiliary spaces.

Kamiseya's dental department is staffed by two dental officers and three dental technicians.

The department provides dental care for Navy and Marine Corps personnel and dependents attached to the U.S. Naval Security Group Activity, Kamiseya, Japan and other subordinate activities under its control. Dental treatment is also rendered for personnel of other Armed Services who are attached to the activity.

CHANGE IN DENTAL TECHNICIAN GENERAL TRAINING PROGRAM

A decided increase in the need for dental technicians coupled with other recent events have dictated that the Dental Technicians School training program be accelerated. To meet this need the clinical phase of the last month of training has been deleted from the General, Class "A", School. Dental Technicians School Trainees no longer will receive a month's clinical training and evaluation by dental officers. They will be assigned to new duty stations with no actual clinical experience. A small percentage of students have proven to have didactic ability but when exposed to the clinical phase were deemed not suitable by their dental officers. To date it has been possible to retain these for further training or to disenroll them if necessary. Since this will no longer be possible, the responsibility for the clinical training will now rest with the dental officer at the initial duty station. It is strongly recommended that the initial assignment of a recent graduate be made with a dental officer most able to provide the patient instruction and understanding that novices require, especially in their first few months. Initial assignments should be made to duties with general duty officers thus avoiding the unique and singular duties often found in the specialties. If possible a few days spent as the second assistant in a busy office will enable an experienced technician to aid in the initial phases of clinical training.

NEW DENTAL JOURNAL

A new journal, titled "Oral Research Abstracts," provides to the dental profession a single source upon which the reader can rely for abstracts of everything related to oral health. This journal is published by the American Dental Association, 211 East Chicago Avenue, Chicago, Illinois 60611. Subscription may be ordered by persons or activities, at $30.00 a year. The journal will be published monthly; each annual volume will have a complete subject index, based on the system used in the Index to Dental Literature.

Oral Research Abstracts is written by scientists for scientists. The abstracts will not be critical reviews; they will be informative, containing data and fact. Each abstract will contain enough information to permit the reader to decide whether he wants to obtain and read the original article.

English language abstracts from all primary dental journals, as well as abstracts of articles related in any way to dentistry, in many non-dental journals, will be published. Oral Research Abstracts will know no barriers of language, discipline or geography; it will present information on all available published material that has pertinence to oral health research. To support this ambitious coverage of the literature, Oral Research Abstracts has about 500 American abstractors, and 53 contributors from the Hadassah School of Dental Medicine in Jerusalem. Concerning the former, it is both interesting and gratifying to observe that Volume 1, Number 1 of Oral Research Abstracts lists 12 U.S. Navy dental officers among the contributing abstractors.

INACTIVE RESERVE OFFICER TRAINING

The following courses and convening dates will be available to Inactive Reserve Officers 2205, for active duty for training during fiscal year 1967 at the U.S. Naval Dental School, National Naval Medical Center, Bethesda, Maryland.

Continuing Education Courses. This training will be taken with officers on active duty. The courses offered are of *two weeks duration* and are as follows:

Removable Partial Dentures	26 Sep — 30 Sep 1966
Fixed Partial Dentures	3 Oct — 7 Oct 1966
Preventive Dentistry	17 Oct — 21 Oct 1966
Oral Pathology	24 Oct — 28 Oct 1966
Endodontics	31 Oct — 4 Nov 1966
Oral Roentgenology	9 Jan — 13 Jan 1967
Oral Surgery	16 Jan — 20 Jan 1967
Complete Dentures	6 Feb — 10 Feb 1967
Occlusion	13 Feb — 17 Feb 1967
Operative Dentistry	24 Apr — 28 Apr 1967
Periodontics	1 May — 5 May 1967

NOTE: In the course that runs from 17 Oct—4 Nov 1966, the officer may have his choice of either Preventive Dentistry and Oral Pathology, or Oral Pathology and Endodontics.

Quota Control:

COMONE	: 1	COMFIVE	: 1	COMNINE	: 3
COMTHREE	: 1	COMSIX	: 1	CNARESTRA	: 1
COMFOUR	: 2				

Eligible dental officers may request orders through their Naval District Dental Officer, or Director of Dental Activities.

LIST OF NEWLY STANDARDIZED ITEMS AVAILABLE FOR ISSUE

FSN	*NOMENCLATURE*	*U/I*	*U/P*
6520–074–4581	Light, Dental, Operating, Field, 110 volt, AC-DC:	EA	193.00
6520–787–2891	File, Periodontal, Orban, No. 12	EA	2.50
6520–890–1883	Case, Dental Instruments, Sterilizing and Storage Corrosion-Resisting Metal	EA	11.90
6520–890–2048	Probe Periodontal Fox	EA	1.48
6520–890–2049	Probe Periodontal Merritt	EA	1.48
6520–890–2050	Curette Periodontal No. 13s-14s, "McCall"	EA	2.50
6520–890–2051	Curette Periodontal No. 17s-18s, "McCall"	EA	2.50
6520–890–2058	Hoe, Periodontal, Orban, No. 5	EA	2.10
6520–890–2059	Hoe, Periodontal, Orban, No. 6	EA	2.10
6520–890–2060	Hoe, Periodontal, Orban, No. 7	EA	2.10
6520–890–2170	Gold Powder-Foil, Pellet, Dent, Assorted sizes	VI	15.90

OCCUPATIONAL MEDICINE SECTION

A FATAL SEQUEL TO GLUE SNIFFING

Arthur S. Blank, Technical Director, Poison Information Center, Connecticut Health Bulletin 80(4): 91-92, April 1966.

A Connecticut teenager was recently found dead under circumstances that pointed to the inhalation of concentrated vapors from a common household dry cleaning product as the cause of death. The young man was known to have indulged in the habit of glue sniffing, and probably, he had become so tolerant of the effects of the solvent vapors from airplane glues or plastic cements, that he required a source of more concentrated solvent vapors in order to achieve the same effect that he had previously obtained from a comparatively small quantity of the adhesive.

The cleaning solvent involved in this incident is commonly used in homes. With reasonable precautions for adequate ventilation, products of this type perform a useful function without causing danger to the health of the user. When misused, with deliberate intent, they can be lethal. The volatile organic solvents in airplane glues and plastic cements are the same ones that exist, in much more highly concentrated form in cleaning solvents, lacquer thinners, and other household and commercial products.

These solvents, along with such substances as chloroform and ether are inhaled by misguided adolescents because the vapors can produce such effects as inebriation, exhilaration, and excitement. The sniffer may then become dizzy and uncoordinated, and his speech becomes slurred. Double vision and buzzing or ringing in the ears occur. Following this, drowsiness, stupor and unconsciousness may develop. The person who sniffs glue regularly often has an unpleasant odor to his breath, which may resemble that of the solvents. Also, excess oral secretions may be produced due to irritation to the mucous membranes of the nose and mouth by the vapors, necessitating frequent expectoration. These youngsters sometimes suffer from chronic nausea, loss of appetite and loss of weight; they may be unusually irritable and inattentive, possibly falling asleep in the classroom.

As the sniffer becomes more tolerant to the effects of the vapors, he requires greater amounts of the glue or plastic cement to induce the same effect. Finally, he may graduate to the use of more highly concentrated sources of vapor such as dry cleaning solvents or lacquer thinners, chloroform or ether.

The volatile organic solvents used in the previously-mentioned products have, for years, been considered hazardous contaminants of the atmosphere when they are used in industrial operations. Although glue sniffers are not, of course, exposed to these solvent vapors continuously, as is the case with those who inhale the vapors at work, the concentrations inhaled by the "sniffer" are usually many times greater than exist in the air breathed by the workers. In industry, care must be used to keep down the concentration of the solvent vapors in the atmosphere because of their toxic effects on the liver, kidneys, brain and blood-forming bone marrow.

There are reasons to believe that persistent glue sniffers will suffer injury from inhalation of these vapors over a prolonged period of time. The chief physician at the Juvenile Hall, Los Angeles County, California Probation Department, states that, "Up to April 29, 1965, we had examined the cases of over 750 glue sniffing children who were admitted to Juvenile Hall by probation officers. Our findings reveal that glue sniffing causes liver, kidney and lung damage, and causes abnormalities in the peripheral blood." More insidious effects of glue sniffing may be expected to develop years later, when natural aging processes or disease bring about deterioration of the body organs. These break-down processes may well be accelerated by latent damage caused years before by the inhalation of toxic chemicals.

While intoxicated by the solvent vapors, many youngsters engage in foolhardy or antisocial activities. There have been reports of youngsters who fell to their deaths from tenement roofs or from piers, and of others who died from suffocation, particularly by plastic bags. It is generally recognized that persistent or chronic glue sniffing is associated with maladjustment of personality. The glue sniffer frequently goes on to more serious forms of addiction such as inhaling concentrated solvent vapors, and then to excessive indulgence in alcohol or narcotics.

SAFE USE OF PESTICIDES

JAMA 190(5): 142, Nov 2, 1964.

Although a recently published book advocated elimination of all pesticide application in the United States, it is apparent that a majority of agriculturists feel that these agents are necessary to our present economy and food production. Therefore, it becomes the responsibility of the general population and of the medical profession to see that these pesticides are used in the safest manner and that appropriate therapy is always available. Pesticide toxicity concerns two major groups of our population: those working directly with the pesticides and their agricultural application, and those having contact because they live in areas where such agents are being applied.

According to date from California, approximately 75% of the systemic poisoning from occupational exposures to agricultural chemicals is due to organophosphorus insecticides, for which diagnostic blood tests are available and specific therapy is effective. A report in a recent issue of the "Archives of Environmental Health" indicates that from 31% to 58% of persons working with pesticides will show evidence of absorption of the organophosphorus compounds. Serious exposures among workers are most common either early or late in the spraying season. Blood tests which show evidence of absorption of insecticides early in the spraying season indicate poor spraying techniques; thus, the workers' spraying techniques must be analyzed and errors corrected immediately. Positive tests occurring late in the season indicate repeated absorption of small doses of insecticide which, if continued, could result in severe symptoms. These individuals should either receive therapy or be removed from further contact with the insecticides.

Simple, rapid, blood cholinesterase evaluation methods are available and are quite accurate in indicating no exposure, moderate exposure, or severe exposure. In Colorado the state health department has placed evaluation kits in key hospitals throughout the state, thus permitting the local physician to make a rapid differentiation between exposure to organophosphorus insecticides and other illnesses. The recent release by the Federal Drug Administration of pralidoxime chloride now provides another specific drug which is effective in the treatment of exposure to the organophosphorus compounds. It is important that information regarding proper dosage and treatment procedures for the use of pralidoxime chloride and atropine be made available to all physicians in each state.

There are a number of procedures which, if adopted in each community, would significantly reduce the exposures encountered. Some serious exposures have occurred among children; therefore, the public should be made aware of their responsibility in locking up all pesticides and in washing out or destroying all empty containers before placing them in the trash. Since a number of serious exposures have occurred among home sprayers who are not aware of the toxicity of the agent used, perhaps sale of these insecticides should be limited to retail outlets where personnel are aware of the proper methods of application and the toxicity of the agents sold. Before commercial spraying of shrubbery near dwellings, occupants should be warned, windows should be closed, and all children and pets kept inside. Workers should not be permitted to wear contaminated clothing home, since several significant exposures of children and spouses have occurred from this source. Because organophosphorus and chlorinated hydrocarbon insecticides are particularly toxic to the liver, persons with known liver disease probably should not work with such pesticides. Generalized community spraying should be done only when designed to eliminate a definite health hazard; efforts should be made by each state health department to acquaint all physicians in the area with the effects of acute insecticide exposure and to make available appropriate blood tests for proper diagnosis. Expert consultation on the proper treatment should be made available on a 24-hour basis.

Further research work should be encouraged, to determine the prolonged toxic effects of small repeated exposures and the effect of the accumulation of these insecticides in the tissues. While the number of workers suffering serious exposure to these insecticides is not large, the majority of exposures can be prevented with proper control techniques. Therefore, it seems imperative that a vigorous effort be made by health agencies and the medical profession to advocate proper use and handling of pesticides and to have proper therapy available should exposure occur.

DEATH DUE TO CADMIUM OXIDE FUMES

H. P. Blejer MD DIH, Berkeley, Calif., Indus Med & Sur 35(5): 363-364, May 1966.

A welder died recently after brazing with a silver alloy which contained Cadmium. This death, due

to acute cadmium fume inhalation and poisoning, is the first of its kind officially reported in our State. An extensive investigation revealed the following important facts.

After six hours' brazing with the silver-cadmium alloy, and over-exposure to and inhalation of cadmium fumes, the welder felt ill. He finished his shift, however, and went home. The next day he felt worse, and did not go back to work. He had developed acute upper and lower respiratory tract symptoms and signs (severe cough and chest pain, dyspnea, and cyanosis), plus systemic ones (malaise, hyperpyrexia). An expert welder, this man attributed all of these to "Welders' Fever", which he had had many times before. Finally, one day after, he was persuaded by a relative to go and see a physician. The welder did not know that the brazing alloy also contained cadmium, and could not tell the doctor. The latter made a diagnosis of chemical bronchitis, and prescribed antibiotic and antitussive therapy for it. Back at home, the welder seemed to improve during the following day. However, less than one day after this, he was found dead in his bedroom, early in the morning.

The total elapsed time between his exposure to the cadmium-brazing fumes and his death was just under four days. The autopsy revealed, among other findings, extreme pulmonary hemorrhagic congestion. Microscopically, lung tissue showed edema, bronchial de-epithelialization, with infiltration of large cells in the small bronchi and the alveolar septa. Polarographic and x-ray diffraction analyses of necropsy tissues and body fluids (for Cadmium, Zinc, Arsenic, Copper, and Antimony) showed, in particular, above-normal and/or poisonous concentrations of Cadmium in lung and urine. Liver and blood were analyzed also. The final diagnoses were: Cadmium Poisoning, Cadmium Pneumonitis, and Pulmonary Edema Due to Cadmium.

A second welder in the same company was also exposed, but much less so, to the same brazing fumes. This occurred a few days after the first welder's death became known. By then certain precautions had been taken: the process had been transferred outdoors, and stationary exhaust ventilation added. The latter was not adequate, however, as the following events show. This second welder developed pulmonary edema also, this time after three days' exposure to the cadmium fumes. At the end of the third day's brazing, he went to see his physician, who admitted him to the hospital that same evening. He recovered fully after three or four days in the hospital, and has remained well since, having returned to his work within ten days. Analyses done on urine and blood collected two weeks after his exposure to cadmium oxide brazing fumes, showed raised concentrations of cadmium in both, although these were not in the lethal range.

Cadmium Fumes are an Extreme Health Hazard

The clinical picture is one typified by the dead welder's history, condition, and findings: extreme irritation of the upper and lower respiratory tract, including the lungs, with extreme coughing, and extreme chest pain, marked dyspnea, and cyanosis. Usually, a marked concomitant hyperpyrexia develops. Generally these have a latent onset—a few hours to one or two days. However, in some cases, they may develop almost immediately after exposure. In such a case, they should not be confused with those of "Welders' Fever" ("Metal Fume Fever," "Zinc Fume Fever," or "Galvanized Metal Fever"), which is markedly less severe and occurs not infrequently among welders. If any of the above develop in any welder brazing with alloys containing cadmium, or in any worker involved with overheating cadmium-containing or cadmium-plated metals, such as some stainless steels, even if the worker does not know that these contain Cadmium, acute Cadmium oxide fume poisoning should be considered in the differential diagnosis, and appropriate treatment instituted. This treatment will be found in standard toxicological and other reference books. Poison control centers may provide necessary information, as shall the Bureau of Occupational Health.

This hazard is not confined just to the spraying, brazing or over-heating of alloys or metals containing cadmium. As mentioned before, this extreme hazard can also arise from the welding, burning, or heating of cadmium-plated steel and other metals. Conceivably, it could arise also from the use in household hobby shops, and the like, from the high-speed drilling of cadmium-plated stainless steels and metals, due to the high temperatures evolved by the drill. The later has not reportedly occurred to this date.

Deaths from acute cadmium poisoning are extremely rare. In the U.S.A. there have been less than 20 reported officially in the last century, and only three reported in the medical literature since 1956. Rutherford T. Johnstone, MD, of Los Angeles, described fully one such death in California, in 1941, prior to any official reporting and recording of such statistics. However, another death

from the same brazing alloy and cadmium fume poisoning has just been reported in Utah, within the last month. It appears that such cadmium-containing brazing alloys are being used more frequently. Another very important fact is that every death reportedly due to acute Cadmium fume poisoning has occurred in industrial workers, especially in welders.

Steps should be taken to ensure proper labeling, and to instruct welders, as well as the welding industry and its suppliers, of the extreme hazard involved, and how to control it.

PSYCHIATRIC DISABILITY AND THE INDUSTRIAL PHYSICIAN

Joseph Lerner MD, Baltimore, Md. JOM 8(5): 257-260, May 1966.

Industrial physicians and psychiatrists are, by the very nature of their intimate association with industry and a large part of the working population, customarily concerned with the practical problems of evaluating disability resulting from physical and/or mental illnesses. In a very practical way, industrial psychiatrists and physicians directly participate in evaluating the problems of disability within the framework of capacity demands of the working situation. Their specific knowledge of a broad spectrum of jobs, with specific capacity demands, places them in an excellent position to correlate the patient's remaining functional capacities with some job assignment.

Clearly, the evaluation of disability varies according to the specific program or agency involved. Industrial psychiatrists perform their psychiatric evaluations on the basis of general psychiatric principles with specific considerations peculiar to the particular industry. This variation in the concepts which underlie the decision as to disability is increased by the fact that in some areas there is a rather broad spectrum of built-in legal and administrative policies.

In industrial medicine, cardiovascular and psychiatric illnesses are the leading causes of disability. Ross, in his report of a study of 40 coal miners, stated: "Psychoneurosis was the most common diagnosis, with pneumoconiosis only second. The number of patients whose disability was entirely psychiatric were almost three times the number of whose disability was entirely physical." Franco studied a series of 704 cases of which almost 20% were of "functional nervous disorders." In our program, individuals with alcoholism, addiction, or other sociopathic patterns are considered ineligible for benefits unless the pattern is associated with a psychosis, psychoneurosis, or organic brain syndrome which has resulted in substantial and persistent loss of functional capacity. Loss of functional capacity is established on what we consider to be parameters of vocational capacity, i.e., the ability to remember, think, communicate, and utilize the emotional and intellectual adjustments incidental to work activity, and the capacity for self-sufficiency. Our criteria are utilized as guides by all state agencies, which make the decisions as to disability.

Under the disability program of the Social Security Administration, the applicant is expected to furnish evidence of a "medically determinable impairment" as the primary cause of cessation of work and as a result of which the applicant has not worked for a period of 6 months. The medically determinable impairment must be considered as being likely to end in death or expected to be of long-continued and indefinite duration. The condition must persist despite acceptable treatment. In contrast with workmen's compensation, the benefits are based upon insured status acquired through earnings as a result of work, but medically determinable impairment need not be work-related. Each case is evaluated on an individual basis and the concept of "the average man" is not used. The disability decision is made on the basis of the evidence on file that a medically determinable impairment is present and that its impact on the function of the applicant, in terms of vocational demands, is so substantial and persistent that the applicant would be unable to perform any kind of work commensurate with his previous vocational experience and educational attainments.

The actual biological level of functional loss is set so as to be incompatible with any substantial gainful activity by most, but not all, individuals. Applicants who continue to work in spite of a severe medically determinable impairment cannot, under the law, be considered eligible for disability benefits. Implicit in this definition of disability under the Social Security program, is that the level of the individual's adjustment (personal, social, and vocational) which existed prior to cessation of work is established as his "norm," since the applicant was able to work in order to acquire insured status at his specific level of adjustment. The existence of a psychiatric illness sufficiently severe to be incompatible with any form of work, lasting 6 months or longer, and expected to be of indefinite duration

in spite of treatment, should be supported by clinical evidence of physiological and/or psychological regression. Such an illness would usually be associated with an unpleasant state for which the applicant would seek relief. In the absence of physiological or psychological regression, we would expect some evidence of substantial and persistent personal and social regression. The evidence should demonstrate the existence of ego regression rather than merely libido regression. The regression should be sufficiently substantial as to materially reduce to effectiveness and the predictability of the applicant's work activity.

Since the primary issue in evaluation of disability under our program is the loss of function resulting from the impact of the psychiatric illness, the diagnosis by itself is inadequate as a basis for a decision as to disability. Under our regulations, the presence of signs and symptoms of a psychosis, a psychoneurosis, or some forms of organic brain syndromes, is not considered necessarily incompatible with any type of significant gainful activity. The facts established on the basis of clinical observations and tests should be consistent with the day-to-day activities of the applicant. The facts of day-to-day activities are an essential part of the frame of reference in mensurating capacity for work. These facts are usually provided by a "report of contact," based on a visit by the applicant to our district office.

Clinical observations as well as clinical tests need to be evaluated with some degree of healthy incredulity. Psychological test results should not be permitted to be the sole basis for the ultimate decision regarding disability.

In the final analysis, the actual day-to-day activities are frequently a reliable frame of reference in which to evaluate the existence of loss of functional capacity, irrespective of what specific diagnosis is made.

In our program, severe overt anxiety reactions are less common than the psychophysiologic reactions. In overt anxiety, we look for clinical evidence of impaired attention span, memory, and powers of concentration, or disturbance of adjustment and behavior. In our program the applications more frequently involve forms of anxiety which are expressed in terms of psychophysiological reactions, as in the second case above. Medical evidence established the presence of a medical impairment—psychophysiological cardiovascular reaction—which resulted in persistent and substantial loss of functional capacity and which could be considered to be of long-continued and indefinite duration in spite of treatment.

In one specific area the decisions pertaining to disability, made by the industrial physician, directly relate to the manner in which psychiatric disability is evaluated under the disability program of Social Security. Many employees who have worked for their companies for many years are retired on disability benefits; in some instances, these individuals apply for Social Security benefits because of their disability. Without considering the various factors utilized by the industrial psychiatrist in making a decision as to disability, it is important to recognize that, although we need the evidence furnished us by the industrial psychiatrist, our decision concerning the existence of disability due to a psychiatric illness is based upon specific legal, administrative, and medical principles which, while not equivalent to those used by the industrial psychiatrist, nevertheless represent the medical approach tailored to the law and administrative policies under which we are specifically required to operate. Thus our decision would not necessarily coincide with that of the industrial psychiatrist.

Much of the difference in approach is related to the fact that while we need the diagnosis of the medically determinable impairment, we focus on the actual clinical evidence of loss of functional capacity, and consider the degree of residual functional capacity in terms of whether it would suffice to enable the applicant to perform some type of gainful work commensurate with his previous education and vocational experience.

SUMMARY

The decision as to psychiatric disability under the Social Security program is based on the existence of a psychiatric illness which has prevented work activity for 6 months or longer, is expected to be of long-continued and indefinite duration despite treatment, and results in persistent and substantial loss of function such that the residual functional capacity is insufficient to permit any type of significant work activity. Loss of function is established on the basis of evidence of psychological, physiological, social, or personal regression. The psychiatric illness need not be work-related, but the diagnosis must be accompanied by clinical evidence of substantial loss of functional capacity.

(The references may be seen in the original article.)

EDITORIAL DESK

BIRTHDAY WISHES TO THE NAVY HOSPITAL CORPSMEN BY GEN. WALLACE M. GREENE, JR. USMC

It is a pleasure for me, on behalf of the United States Marine Corps, to extend congratulations and best wishes on the sixty-eighth anniversary of the Navy Hospital Corps.

Since the establishment of the Hospital Corps in 1898, Corpsmen have served the Navy and Marine Corps with great distinction throughout the world. Their professional skills and courage have won for them the respect and admiration of military personnel everywhere.

Members of the Hospital Corps are making a vital contribution to our country's efforts in Vietnam. Not only are they taking excellent care of sick and wounded Marines, but they are helping treat the people of South Vietnam through the Civil Action Program, and in so doing they have won us many friends and have helped the Vietnamese people to better understand our country's objectives.

NAVY NURSES AT SEA— YESTERYEAR AND TODAY

On 13 May 1966, Navy nurses serving all over the world celebrated the fifty-eighth anniversary of the Navy Nurse Corps. This year's anniversary serves as a symbolic bond between Navy nurses serving aboard ship today and the pioneer nurses of the Navy Nurse Corps, the Sisters of the Order of the Holy Cross.

Since January 1966, Navy nurses have been assigned and are serving on the Navy's newly recommissioned Hospital Ship, the USS REPOSE in the Vietnam area. In contrast, their pioneer Sisters served aboard the Navy's first Hospital Ship, the USS RED ROVER in the Civil War era.

On 24 December 1862, three Holy Cross nuns boarded the USS RED ROVER to care for the sick and wounded seamen. These pioneer women were Sister Veronica Scholl, Sister Callista Pointan and Sister Adela Moran. A fourth nun, Sister St. John, joined their ranks in February, 1863. Two negro nurses were among the lay women who served under the direction of the Sisters. In 1962 the U.S. Navy recognized these Sisters of the Holy Cross of Saint Mary's Notre Dame of South Bend, Indiana as the forerunners, or pioneers, of the Navy Nurse Corps. The Holy Cross Sister Nurse Veterans were further honored in the dedication of a Civil War Memorial on the grounds of Saint Joseph's Hospital, South Bend, Indiana in 1965. The memorial plaque cited that "eighty of the Sisters of the Holy Cross served as military nurses. The Sisters became the forerunners of the Navy Nurse Corps in 1862 when they boarded the USS RED ROVER, the Navy's first hospital ship."

Recently the Library of Congress forwarded to the Bureau of Medicine and Surgery, Navy Department copies of letters penned in 1865 and 1866 by Sister Angela of Saint Mary's, Notre Dame, Indiana and Sister Angela of Holy Cross, St. Mary's. Both letters were addressed to the Fleet Surgeon, Ninian A. Pinkney. These letters and a letter from Fleet Surgeon Pinkney to Sister St. John (as it appeared in the Journal Courier, Jacksonville on 23 December 1962) are quoted below.

"Saint Marys
Notre Dame P.O.—Ind
January 17 '66 (1866)

"Fleet Surgeon Pinkney
Miss Flotilla

"Honored and Esteemed Sir:

"Your favor of August 5th has just been received and I hasten to inform you that I have not the slightest inclination to remove our Sisters from the Red Rover provided they are enabled to attend Mass—(as they do at present).

"It was a deep source of regret to me when I feared we might have to do it—merely because the nature of the boats movements would continue to prevent the fulfillment of one of our essential duties —But as this obstacle is removed I am rejoiced to have them stay as long as their services are needed.

"Permit me to make use of this occasion to thank you most cordially for your great kindness to our Sisters.

"Through them I have learned to know and esteem Dr. Pinkney as one of the best and most devoted of the noble Corps composing the Navy—And with

these sentiments of respect and esteem permit me to sign myself your obedient servant and friend in behalf of the sick and suffering of the Navy."

"Sister Angela
of Holy Cross"

St. Marys August 11th '65' (1865)

Fleet Surgeon Ninian A. Pinkney wrote to the chief nurse at the Pinkney Naval Hospital, Memphis, June 9, 1865, shortly after the war was over:

"My dear Sister St. John,—Will you do me the favor to forward to Mother Angela with the best regards of Fleet Surgeon Pinkney the enclosed emblem (a gold cross), as an evidence of his high appreciation of one who has the honor to represent as its head the noblest of the good ones of the earth.

"I expect to arrive in Memphis about the 18th. The Hospital, I think, will be kept in motion a little longer, and the Red Rover put out of commission."

"Dr. Pinkney, USN
Easton, Md."

"Most Honored and Esteemed Sir

"I have just ascertained, through the Dead Letter Box, that my reply to your most courteous note of June 9th enclosing such a beautiful testimonial of friendship and esteem was never received by you—Therefore I hasten to acknowledge at this late date my high appreciation to your exquisite favor—received through Sister Saint John, which I shall ever prize as the memento of one who holds so high a place in the esteem of all the Sisters of Holy Cross—as Fleet Surgeon on the Mississippi during the terrible National Contest of the last three years—With most profound considerations of regard."

"I have the honor to be
Your friend and humble servant"
"Sister N. Angela"
—Nursing Div, BuMd.

U.S. NAVAL SCHOOL OF HOSPITAL ADMINISTRATION CLASS NUMBER 27 GRADUATES

Thirty-six officers of the Medical Service Corps, U.S. Navy, completed the program of instruction in hospital administration on 10 June 1966.

Shirley C. Fisk MD, Deputy Assistant Secretary of Defense (Health and Medical), addressed the graduates and gave a most enlightening and stimulating talk on the current and proposed legislation and other dynamic factors challenging the military hospital administrator of today. He stressed the need for highly trained Medical Service Corps officers with leadership responsibility and imagination to meet this demand.

The Commanding Officer, National Naval Medical Center, RADM Cecil L. Andrews MC USN, awarded the graduation certificates, and the Chief of the Navy Medical Service Corps, CAPT Robert S. Herrmann MSC USN, delivered the class charge.

The Deputy Chief, Bureau of Medicine and Surgery, RADM R. O. Canada MC USN, presented the United States Navy Surgeon General's Annual Award for Scholastic Achievement to LT John R. Kozik MSC USN, at the graduation ceremonies. The award is based on academic achievement, overall application and qualification.

Established on 2 August 1945, the U.S. Naval School of Hospital Administration, commanded by CAPT E. L. Van Landingham, Jr. MSC USN has its primary mission to provide advanced instruction in the modern theory and practice of hospital administration, for the Medical Service Corps officers of the U.S. Navy and such other officers as may be assigned. Since its inception, 1,102 students, consisting of 1,023 U.S. Naval Officers, 9 U.S. Army Officers, 56 U.S. Air Force Officers, and 14 foreign officers have graduated from the School.—Public Affairs Office, NNMC, Bethesda, Md.

EDITOR'S NOTE

Pseudotumor Cerebri: A Historical and Clinical Review by LCDR B. L. Rish MC USN and William F. Meacham MD appeared in the Journal of the Tennessee Medical Association 58(11): 355–361, November 1965. Recurrent Pseudotumor Cerebri in Pregnancy was the title of a report reprinted in the U.S. Navy Medical News Letter 47(7): 6, 8 April 1966 by two Naval Medical Officers.—Editor.

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